DISSERTATION ON

A STUDY OF STRENGTH OF ASSOCIATION BETWEEN CHANGES IN SERUM URIC ACID, SERUM CALCIUM, URINE ALBUMIN CREATININE RATIO AND PRE ECLAMPSIA AND ITS IMPACT ON OUTCOME.

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CERTIFICATE

This is to certify that this dissertation entitled "**A STUDY OF STRENGTH OF ASSOCIATION BETWEEN CHANGES IN SERUM URIC ACID, SERUM CALCIUM, URINE ALBUMIN CREATININE RATIO AND PRE ECLAMPSIA AND ITS IMPACT ON OUTCOME.**" is bonafide original work of **DR.M.KOKILAVANI** in partial fulfilment of the requirements for M.S. Branch II (Obstetrics And Gynaecology) Examination of The Tamilnadu DR. M.G.R Medical University to be held in APRIL 2015. The period of study was from September 2013 to august 2014.

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DECLARATION

I, Dr.M.KOKILAVANI, solemnly declare that dissertation titled "**A STUDY OF STRENGTH OF ASSOCIATION BETWEEN CHANGES IN SERUM URIC ACID, SERUM CALCIUM, URINE ALBUMIN CREATININE RATIO AND PRE ECLAMPSIA AND ITS IMPACT ON OUTCOME."** is a bonafide work done by me at Thanjavur Medical College, Thanjavur during September 2013 to August 2014 under the guidance and supervision of **PROF.DR.E.KALARANI MD,DGO**, Head Of The Department, Department Of Obstetrics And Gynaecology, Thanjavur Medical College, Thanjavur.

This dissertation is submitted to Tamilnadu Dr. M.G.R Medical University towards partial fulfilment of requirement for the award of **M.S. Degree (Branch II) in Obstetrics And Gynaecology.**

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TABLE OF CONTENTS

LIST OF TABLES

LIST OF CHARTS

ABSTRACT

BACKGROUND

Hypertensive disorders of pregnancy complicate almost 7-10% of all pregnancies. The development of hypertension and proteinuria after 20wks of gestation is referred to as pre eclampsia. It is a major cause of maternal morbidity andmortality and is also associated with increased perinatal problems.

Recent studies have shown the relationship between the aggravation of Thehypertensive complications and the change in concentration of various chemistries inmothers serum. Interestingly, variable serum calcium, magnesium and uric acid levelsare found in pre-eclamptic mothers.

Studies have also demonstrated the diagnostic value of Albumin Creatinineratio (ACR) in a single voided urine sample for quantification of proteinuria,compared to those of 24 hours of sample in patients with pre-eclampsia.

OBJECTIVES

1. To estimate the strength of association between the changes in the serum uric acid, serum calcium, urine albumin creatinine ratio in pre eclampsia.

2. To know whether these factors in pre eclampsia influence on maternal and perinatal outcome.

Materials and Methods

The study included 50 pre-eclamptic patients, and 50 normal pregnant Women in the age group of 18-35 yrs between 28 – 32 weeks. Serum calcium, uric acid and spot urinaryalbumin creatinine ratio were estimated in these subjects.

Serum calcium was estimated by Arsenazo-III, Serum uric acid was estimated byenzymatic colorimetric method, Urinary albumin was estimated by immunoturbidimetricmethod and Urinary creatinine was estimated by colorimetic method.

Results

The serum calcium in pre-eclamptic women was significantly lower (8.29 ± 0.69mg/dl), in comparison to controls whose value was 9.73 ± 0.72mg/dl($p<0.001$)) and serum uric acid in pre-eclamptic women was significantly higher (6.7 ± 1.7 mg/dl) in comparison to controls whose value was 4.26 ± 1.03 ($p<0.001$). The Urinary albumin/creatinineratio in pre-eclamptic women was significantly higher (157.8± 48.7 mg/g) in comparison to controls whose value was (28.1± 25 .1 mg/g) ($p<0.001$).

Conclusion

In pre-eclampsia, the serum levels of calcium, magnesium, uric acid are altered, and spot UACR is significantly increased, suggesting strong association between these factors and severity of pre-eclampsia.

Thus it can be concluded that , the careful monitoring of these markers in pregnant women may help in the mortality and morbidity reduction and thereby helpful in the favourable outcome of the pregnancy.

Key words

Serum calcium, uric acid, urinary albumin-creatinine ratio, microalbuminuria, pre-eclampsia, pregnancy induced hypertension.

INTRODUCTION

Pregnancy is the most important period in women life, but it can be dangerous also. Pregnancy is a physiological state with profound alterations in biochemical and mechanical process. If the pregnancy has no complications, the biochemical changes are reversible soon after delivery[1]. Hypertension and proteinuria are the important complications of pregnancy[2].

Pre eclampsia is defined as the presence of systolic blood pressure more than 140 mm of Hg and diastolic pressure more than 90 mm of Hg , along with proteinuria , edema or both in a pregnant women . It usually occurs after 20th weeks of pregnancy or sometimes earlier when there is multi-fetal pregnancy or extensive hydatiform changes in the chorionic villi[3.]

It normally occurs in about 5- 10 percentage of pregnancies. It is a pregnancy specific disease and is associated with high maternal and fetal morbidity and mortality. Pre eclampsia once developed is progressive till delivery.

“Berg and colleagues reported that 16% of 3201 maternal death in the united states from 1991 to 1997 were complications of gestational induced hypertension . During this study, black women had 3% times higher mortality compared with the white women.[4]

Pre eclampsia in its severe form may be associated with cerebral or visual disturbances , oliguria , elevated serum creatinine & serum uric acid along with the presence of epigastric pain.

The blood pressure elevation may be the most important tool for the identification of the pre eclamptic women. The peripheral edema may occur thereafter. The regular blood pressure recordings are essential for clinching the pre eclamptic women.

The visual disturbances , although not a very common presentation, but it may occur as a result of pre eclampsia in the pregnant women. But once visual changes accompanies the elevated blood pressure and proteinuria or edema , it rings the alarm for the presence of pre eclampsia.

These changes when accompanied with convulsions without pre existing neurological disease like epilepsy and it may lead to eclampsia. When the seizures accompanies the elevated blood pressure , proteinuria or edema , it may result in eclampsia.

The pathophysiological mechanism is characterized by a failure of the trophoblastic invasion of the spiral arteries, leading to the maladaptation of the maternal spiral arterioles which may be associated with increased vascular resistance of the uterine artery and decreased perfusion of the placenta[5].

The spiral arterioles plays an significant role in the pre eclampsia. The structural and physiological changes in the normal spiral arterioles may lead to the development of the pre eclampsia.

The progression of the pre eclampsia with the cerebral, vascular and the changes in the uric acid levels explains its severity. The peripheral edema in the pre eclamptic women is due to the altered albumin levels and it leads to oncotic pressure changes and so the edema.

The precise cause of the vascular endothelial dysfunction , an important factor in the pathophysiology of pre eclampsia remains unknown[6].

The reults from many clinical studies show the relationship between the aggrevation of hypertensive complications and the change in concentration of various chemicals in mother's serum. Interestingly , variable levels of serum calcium and serum uric acid levels are found in pre eclamptic mothers[7,8].

The lowering of serum calcium and increase of intracellular calcium can cause an elevation of blood pressure in pre eclamptic mothers.

Besides serum calcium hyperuricemia is believed to result from the decreased renal excretion that occur as a consequence of the pre eclampsia, also increased production may be secondary to tissue ischemia and oxidative stress[9,10].

Soluble uric acid impairs nitric oxide generation in the endothelial cells. Hyper uricemia induces endothelial dysfunction and may induce hypertension and vascular disease.

Therefore the alteration of calcium and uric acid during pregnancy could be one of the potential causes of pre eclampsia.

Besides the blood pressure monitoring, urine albumin creatinine ratio also helps in the prediction of the pre eclamptic women. The pre eclamptic women urine sample is usually loaded with microalbumin and the creatinine. This helps in the detection of pre eclampsia .

The studies have also demonstrated the diagnostic value of the albumin/creatinine ratio in a single voided urine sample for quantification of proteinuria compared to those 24 hours of sample in patients with pre eclampsia[11].

Hence in this study, we propose to estimate and compare the serum levels of calcium ,uric acid and urinary albumin – creatinine ratio in normal pregnant women and pre eclamptic women.

Maternal complications include

- Abruptio placenta
- Acute renal failure
- HELLP

- Convulsion
- Occipital lobe blindness
- Pulmonary edema
- Possible complications of caesarean sections

Fetal complications include

- Prematurity
- Intrauterine growth retardation
- Intrauterine death
- Fetal distress

The complications of severe pre eclampsia could be prevented by prompt diagnosis of high risk patients, antenatal care and timely intervention.

The fetal risks are very severe when the albumin and the creatinine levels are largely altered. The coagulation pathway also gets stimulated if endothelial injury occurs.

When the pre eclampsia sets in a very early trimester , close monitoring of the pregnant women is necessary. If the pre eclamptic women is on regular follow up and prompt medications the risks are greatly reduced. The utero placental circulation is also safeguarded by controlling the blood pressure.

The low platelet count in the pre eclamptic women may results in the severe bleeding tendancies. It occurs as a result of the alterations in the

coagulation factors and fibrinogen. When this stage sets in the maternal and fetal lives are at great risk. The periodic monitoring of the maternal serum for the platelet level and hepatic enzymes explains the necessity for avoiding complications.

Termination of pregnancy is the treatment of severe pre eclampsia. The risk of the fetal and maternal lives are more in the continuation of pregnancy. So termination is usually preferred in this situation. The possibility of progression of pre eclampsia to eclampsia is also more in uncontrolled hypertension.

The identification of the women at risk of pre eclampsia is essential in the antenatal period. The prompt treatment at the initial stage may prevent severe morbidities for both mother and baby.

The identified cases of pre eclampsia should be on a regular follow up. It is usually advised for regular blood pressure monitoring , blood and urine tests from the first trimester itself. This is because pre eclampsia usually occurs in 2^{nd} trimester in many pregnant women. But in rare cases it starts from the first trimester also.

There are several methods to identify the women who are at risk of pre eclampsia which includes roll over test, isometric hand grip exercise test, angiotensin II pressor response and mean arterial response test. However , these

tests have certain limitations for screening because of false positive results and subjective nature of result interpretation.

Pregnancy induced hypertension complicates 5-10% of all the pregnancies. In the developed countries, 16% of the maternal mortality isdue to hypertensive disorders. Therefore early detection of pregnancy induced hypertension &appropriate management is a must to decrease both maternal and perinatal morbidity and mortality.

REVIEW OF LITERATURE

REVIEW OF LITERATURE

HISTORY

The history of eclampsia starts from Hippocratic writings(430-330 BC). In the year (384 – 322 BC) Aristotle was the first to realise that the fetal nutrients are transferred through the umblical cord , which is the only source of connection between the mother and fetus. He also realised that the fetus is fully surrounded by membranes. De-La Motte , in the year 1726, considered that unless associated with convulsions , the oedema is mostly benign[37].

During 18th century, the idea of proteinuria linked with eclampsia was identified and in the same period, the association between the oedema, headache and blurred vision were also remarked.

In the 19th century, the pre eclampsia was studied in a large manner. As a result of these researches, hypertension was identified as an important factor in the pre eclampsia. The triad of oedema, hypertension and proteinuria which often precedes the convulsion was came to known as pre eclampsia.

In the year 1924, renowned scientist husselman identified that a primigravida is eight times more prone to have eclampsia in her pregnancy than multigravida. He also found there isa six fold increased risk of eclampsia in twin pregnancy.

In the year 1926- 1936, Herrick and co workers found that the essential hypertension is a highly associated factor in the hypertensive disorders of pregnancy.

Dickmann 1952, found that when hypertensive disorders are present in a pregnant woman, she may have either nephritis or essential hypertension.

Redman 1991, attributed pre eclampsia to be an inadequate response of the mother to the fetus. Gill in 1994, postulated the familial nature in the pre eclampsia patients[38]

Ferrazzani and coworkers reported that the perinatal morbidity and mortality increased with the combination of proteinuria and hypertension. Their study was based on the proteinuric pregnant women and their pregnancy outcomes. 444 pregnant women were studied. They found that there was a four fold increase in perinatal mortality rate in proteinuric pre eclampsia than in the chronic hyper tension and non proteinuric gestational hypertension.

Ginsberg et al , in his researches found that the amount of protein excreted in the urine is of diagnostic importance.

Pederson EB and co workers in 1984, worked on the serum calcium in (1)normal preganant women, (2) patients with pre eclampsia and (3)non pregnant control subjects[39]. Serum calcium was reduced in pre eclampsia, the serum calcium was not differed markedly when compared with normal pregnant

group. It was concluded that both normal pregnancy and pre eclampsia have significant variations in calcium metabolism.

Saudan et al in their study have emphasized the need for quantitation of proteinuria. The morbidity increases with the nephrotic range proteinuria.

Rodriguez H M and coworkers (1988), examined first morning urine sample in 88 normotensive gravid women between 24 to 34 weeks for the presence of microalbuminuria[40]. Receiver operator curve was used. Pre eclampsia was predicted using the value of 11µg/ml. Albumin level of ≤ 11µg/ml was found in five on ten pregnant women who developed pre eclampsia and also on fourteen normotensive pregnant women. the test gave a specificity of 99%, sensitivity of 50%, PPV of 83% and NPV of 94%.

Oscar E and coworkers(1990), examined protein/creatinine (mg/g) ratio in random urine samples. The study people included were 35 pre eclamptic women and 70 healthy pregnant women[41]. The ratio did not exceed 200 mg/g in any of 70 healthy pregnant women and therefore ratios below this value can be considered as normal.

Misiani R and coworkers (1991), examined if the microalbuminuria could be an early reliable indicator for the pregnancy induced hypertension to evaluate the effects of physical activity on the excretion of albumin in normal pregnancy and pregnancy induced hypertension[42]. The study was done on 67

healthy primi gravidae , from 16 to 36 weeks of gestation and 12 weeks of post partum. Among which, 55 completed normal pregnancy and 12 developed pregnancy induced hypertension. The day time urinary albumin excretion was found to be significantly higher in the pregnancy induced hypertension developed patients(p value between less than 0.005 and less than 0.001) than in normal primigravidae (p value between less than 0.01 and less than 0.001). The hypertension developed after the urinary albumin is found to be increased.

Kenneth higby and co workers 1994, measured the normal 24 hour excretion values of urinary albumin and total protein in healthy pregnant women[43]. 260 mg/ 24 hour of urinary protein and 29 mg/24 hour of albumin as the upper limit of normal pregnancy was supported by this data.

Phillip N baker and co workers (1994), examined both urinary albumin creatinine ratio and urinary calcium/ creatinine ratio from single void urine of 500 normotensive nulliparous women at 19 weeks of gestation[44]. The result was found to be not with much differences in these two ratios in the preeclampsia patients and normotensive patients.

Risberg A and co workers (2004) , researched for the measurement of spot urine albumin creatinine ratio to be a alternative to the dipstick and the wastage of time in 24 hour urine samples examinations. 24 hour urine samples were collected in 12, 24 and 36 weeks of gestation from (1)normal pregnant women, (2)who developed pre eclampsia during the study, and (3) PIH

pregnant women at the time of entering the study[45]. Microalbuminuria was found to be in three persons among PIH group and two persons in normotensive group. Severe albuminuria (>300mg/24 hours) was seen in one of the 46 normotensive patients(2%) and in 3 of the 19 PIH patients(16%). The albumin excretion in the urine was identified by the albumin creatinine ratio during pregnancy. The results found that the urinary albumin creatinine ratio was found to be an better alternative to the 24 hour urine collections.

Neithardt et al , in his study on 30 pregnant women, for the prediction of pre eclampsia by the single void urine protein creatinine ratio as an alternative to the 24 hours urinary protein sample estimation. In this study, it was clealy stated that the estimation of 24 hours urinary protein might be a cumbersome and time consuming job. The 24 hours urine sample collection was started before mid day and blood for creatinine at the same time. A single void urine sample collected after 24 hours sample collection immediately. Biuret test for protein and Jaffe's test for creatinine. The conclusion was there is a significant association in both the tests with a $r = 0.93$ and $p < 0.001$ and the protein creatinine ratio was also useful .

Ginsberg et al explained the merits of single void urine sample protein creatinine estimation over the 24 hours sample collection in a stable GFR pregnant women.

Nissel H and co workers (2006) measured for the accuracy of spot urine albumin/ creatinine ratio in pregnant women with hypertension.urine albumin creatinine ratio and albumin excretion >300mg /day were examined in 54 pregnant women with hypertension[46]. The study shown that the stastically cut off value of 27mg/mmol was closely related with 24 hours urinary albumin excretion. It was shown that the spot urine albumin / creatinine sample examination could be a better alternative to the 24 hour urine sample collection.

Frank p.schubert and co workers (2006) measured random protein /creatinine ratio as a predictor of significant proteinuria (≥300mg/24 hour) for the evaluation of pre eclampsia. A protein/creatinine ratio of ≤0.15 rules out significant proteinuria and may easily clinch the pr eclampsia[47].

Daya sirohiwal and co workers (2009), evaluated the 24 hours urinary protein and calcium in the prediction of pre eclampsia. 200 normotensive pregnant women were examined[48]. Among which, 21 women developed pre eclampsia. In that 21 pre$ eclamptic women, 13 were of mild pre eclamptic type and 8 were of severe pre eclampsia. The pre eclampsia was more prone in women with increased 24 hour urinary protein level.

Roberts J M (1997 - 2002) studied on 972 pregancies in a nested casse control study and reported that the hyperuricemia is an important tool for diagnosing gestational hypertensive disorder of pregnancy as equal to proteinuria.

Punthumapol C and kittichotpanich B (2006- 2007), in their studies, reported that there is a significant association of increased serum uric acid level and pre eclampsia[49].

Johnson RJ et al (2003), assessed the link between the vascular disease and uric acid level and proposed the possible mechanisms of the uric acid effect in the endothelial dysfunction by inducing anti proliferative effects and impairing nitric oxide synthesis, inducing the vascular smooth muscle proliferation and synthesis of C reactive protein, increasing platelet adhesiveness and lysis, thrombus formation, oxidative stress and free radical formation and lipid peroxidation[50,51].

Bainbridge S A et al (2009) , studied the pre eclamptic patient's uric acid levels and reported the elevations in the circulating uric acid plays vital role in the disease pathology through the attenuation of trophoblastic invasion and vascular remodelling in spiral arteries[52].

Saleh F et al (2010) conducted case control study and reported that the elevated serum uric acid levels plays a vital part in detection of pre eclampsia[53].

Hawkins TL-A et al (2011) studied on the role of uric acid levels in the maternal and fetal outcome. They reported that hyperuricemia is an important finding in predicting adverse outcome and its role in women with gestational hypertension without any feature of pre eclampsia[54].

They concluded that the serum uric acid examination in the pregnant women is an useful and inexpensive marker of predicting preeclampsia and fetal growth restriction.

Chanvitya and co workers (2006 – 2007) studied on the pre eclampstic mothers and found the serum levels of calcium is decreased. Hypocalcemia was also an important factor in the pathogenesis of pre eclampsia[55].

Idogun ,Imarengiaye , momoh (2007) did a study on the calcium levels in pregnant women and found that the calcium levels of pre eclamptic women were found to be reduced[56].

Sukonpan and phupong v (2005) , in their study on 40 pre eclamptic women and 40 normal pregnant women, found that hypocalcemia is present in the pre eclamptic women serum[57].

Selhattin kumurul and co workers (2002) studied on the calcium and its role in the pre eclamptic mothers and found that hypocalcemia is present in the maternal serum[58].

Geeta krishnamoorthy B (2000- 2002) did a study on women withmild pre eclampsia (121) and severe pre eclampsia (26) women and found the decrease in the maternal serum calcium levels[59].

Klaus and co workers (1998) studied on the serum calcium levels of 16 pre eclamptic women and 18 normal pregnant women. They found the reduced calcium levels in pre eclamptic women[60].

Standley CA, Whitty JE, Mason BA (1997), studied on 31 pregnant ladies in first, second, third trimester out of which nine who developed pre eclampsia showed no change in the calcium levels[61].

Naser O, Malas and co workers (1998 to 2000) did a study on 40 pregancy induced hypertension women an 40 normal pregnant women. once the patient newly developed hypertension in third trimester, and fulfilled the selected criteria she was enrolled in this study. The mean calcium level in the hypertension developed women was (8.22 ±0.12 mg%) when compared with normal pregnant women(9.50±0.16 mg %)[62].

Golmohammad lou and co workers studied on 52 women with pre eclampsia in their third trimester and 52 normal pregnant women.They concluded mean serum levels of calcium , magnesium , copper and zinc are not significantly altered in the pathogenesis of pre eclampsia[63].

Seema jain and her co workers did a study on the calcium , magnesium, and zinc levels in 50 pre eclamptic cases and normotensive controls. Result came to be decreased levels of calcium in the pre eclamptic women[64,65].

HYPERTENSIVE DISORDERS IN PREGNANCY

- ✓ Historically , this disorder was reported nearly 2000 years back when celus reported as seizures in pregnant women that occur after delivery.
- ✓ This abnormality was given the name “ECLAMPSIA” in greek which means lightening , because of its rapid and unexpected appearance[12].
- ✓ In the middle of 1800s,urinary examination of proteins in pregnant women with eclampsia revealed that severe proteinuria may antedate the seizure.
- ✓ In the later part of 1800s, when it become possible to measure blood pressure with sphygmomanometer, it is apparent that, like proteinuria, in eclamptic women, high blood pressure also antedated the seizures[13].
- ✓ The term pre-eclampsia was applied as proteinuria and hypertension which antedated eclampsia.

Hypertensive disorder complicating pregnancy are common and form one of the deadly triad, along with haemorrhage and infection, that continues to be responsible for increased maternal morbidity and mortality related to pregnancy.

The identification of the pre eclamptic pregnant women should be done as earlier as possible. Treating the pre eclampsia at the initial stages is easier when compared with treating those with complications.

Enhanced surveillance will help in diagnosing high risk pregnant women and the early detection and prompt treatment helps to prevent progression of the disease. Correct treatment at the early stages of the disease will help in good pregnancy outcome for both mother and fetus. However why pregnancy induces this vascular disease remains an unsolved problem in obstetrics.

CLASSIFICATION[14]

According to working group of National High Blood Pressure Education Program (2000) , hypertensive disorders complicating pregnancy are classified into 5 types

1. Gestational hypertension
2. Preeclampsia
3. Eclampsia
4. Pre-eclampsia superimposed on chronichypertension
5. Chronic hypertension

An important feature of this classification is that it differentiates pre-eclampsia and eclampsia from other hypertensive disorders of pregnancy.

GESTATIONAL HYPERTENSION

It is defined as

- ✓ Recording of systolic blood pressure ≥140 mm hg or diastolic blood pressure ≥ 90 mm hg first time in pregnancy after 20 weeks of gestation.
- ✓ Not accompanied by proteinuria.Blood pressure returns to normal within 12 weeks of postpartum period.

PRE- ECLAMPSIA

It is defined as

- ✓ Rise in blood pressure with proteinuria, edema may be present.
- ✓ Proteinuria ≥ 300 mg per 24 hrs urine collection or 30 mg /dl. That is equivalent to 1(+) in dipstick tests in random urine samples

It is classified in to two types,

- ✓ Mild pre eclampsia
- ✓ Severe pre eclampsia

Pre eclampsia is considered as severe if any of the following is present

- ✓ Systolic blood pressure ≥ 160 mm hg or diastolic blood pressure ≥ 110 mm hg.
- ✓ Proteinuria 2.0 gm per 24 hrs urine collection samples.

- ✓ ≥ 2 (+) in dipstick random urine samples.
- ✓ Thrombocytopenia (platelets <1 lakh /µL)
- ✓ Symptoms like persistent headache, visusal distubances, epigastric pain.
- ✓ Microangiopathic hemolysis- increased lactate dehydrogenase
- ✓ Serum creatinine elevated
- ✓ Pulmonary edema
- ✓ IUGR or Oliguric pregnant women.

ECLAMPSIA

This occurrence of generalised tonic clonic type of seizures in a women with pre eclampsia is termed as eclampsia. It may not be attributed to other cause. It may occur before, during or after delivery.

PRE ECLAMPSIA SUPERIMPOSED ON CHRONIC HYPERTENSION

New onset of proteinuria in a women with chronic hypertension after 20 weeks of gestation

CHRONIC HYPERTENSION

- ✓ Blood pressure ≥140/90 mm hg before 20 weeks of gestation or before pregnancy.
- ✓ Diagnosed as hypertension after 20 weeks of gestation and persistent after 12 weeks postpartum.

INCIDENCE AND RISK FACTORS

Pre eclampsia commonly affects young and nulliparous women. Incidences varies from 3 – 10 % in nulliparous women. Incidence of preeclampsia in multiparous women is less than that of nulliparous.

RISK FACTORS

- Genetic predisposition – family h/o pre eclampsia
- Age > 35 years
- Interval from last pregnancy >10years
- Obesity BMI> 35 kg/m^2
- Multifetal gestation
    - GHT – 13 versus 16% in singleton pregnancy
    - Pre eclampsia – 13 versus 5 % in singleton pregnancy.
- Hydraminos
- Vesicular mole
- Hydropsfetalis
- Chronic hypertension.
- Maternal diabetes.
- Renal disorders.
- Antiphospholipid syndrome
- Systemic lupus erythematosus
- h/o smoking and abnormal uterine artery Doppler at 18 to 24 weeks.

Age

Compared to younger women there is greater incidence of pre eclampsia in women older than 35 years. The incidence of pre eclampsia is 9.4 percentage in women >35 years old when compared with 6.4% in women <35 years old. After 34 years, there is increase of 30% risk of pre eclampsia for every year thereafter.

Genetic factors

In 1873, Elliot described the familial nature of the disease which was reviewed by chesley in the year 1968. He reported a patient who died of eclampsia. Both father and mother contribute to the genetic risk. There is presence of increased susceptibility of inherited genes from the pre eclamptic mother to the foetuses, which are capable of triggering pre eclampsia. It is a multifactorial polygenic syndrome. Some of the genes responsible for this are

- MTHFR gene affecting methylene tetra hydrofolate reductase
- Factor V(leiden) gene
- Angiotensinogen gene(AGT)
- HLA genes causing immunological tolerance
- NOS_3 gene affecting endothelial nitric oxide production
- F2 (prothrombin factor II) gene
- ACE (Angiotensin converting enzyme) gene.

ETIOLOGY

Inspite of the researches over the years, the exact cause of pre eclampsia remains unknown.Gestational hypertension disorders are very much likely to develop in women who[15]

- Are exposed to chorionic villi for the first time
- Are exposed to super abundance of chorionic villi , as with twins or hydatiform mole.
- Has pre existing vascular disease
- Are genetically predisposed to hypertension developing during pregnancy.

According to sibai (2003), the potential causes include the following

- Abnormal trophoblastic invasion of uterine vessels.
- Immunological intolerance between maternal and fetoplacental tissues.
- Maternal maladaptation to cardiovascular or inflammatory changes of normal pregnancy.
- Dietary deficiencies.
- Genetic influences.

IMMUNOLOGICAL THEORY

The possibility that immunological as well as endocrine and genetic mechanisms are involved in the genesis of pre eclampsia. The risk of pregnancy induced hypertension is enhanced in circumstances where formation of blocking antibodies to antigenic sites on the placenta might be impaired or where the number of antigenic sites provided by the placenta is unusually great when compared with the amount of antibody as with multiple fetuses.

However some studies found no association of compliment fractions c3, c3F with pre eclampsia.

GENETIC THEORY

In the year 1979, cooper and liston revealed that preeclamsia is dependent upon a single recessive gene, but multifactorial inheritance cannot be excluded.

DIETARY DEFICIENCY

Some of the workers implicated that the calcium deficiency might be one of the cause of pre eclampsia. Studies have reported that dietary supplements of 2gm of calcium per day after mid pregnancy reduce the incidence of preeclampsia.

PATHOGENESIS

Women with pre eclampsia show changes in the vasomotor activity, plasma volume and coagulation system. Their disturbances had been attributed to the endothelial cell activation or dysfunction.

- ***VASOSPASM[16]***

The basic pathophysiology of pre eclampsia and eclampsia is vasospasm. Vasoconstriction causes resistance to blood flow and leads to the development of arterial hypertension.

- ***ABSENCE OF SPIRAL ARTERIES REMODELLING***

"The inciting organ in the development of pre eclampsia is placenta"

Uteroplacental vessels development proceeds into two stages

  - First stage
    - before 12 weeks post fertilisation : upto the interface between decidua and myometrium
  - second stage
    - between 12 to 16 weeks. It involves invasion of intramyometrial segments of spiral arteries.

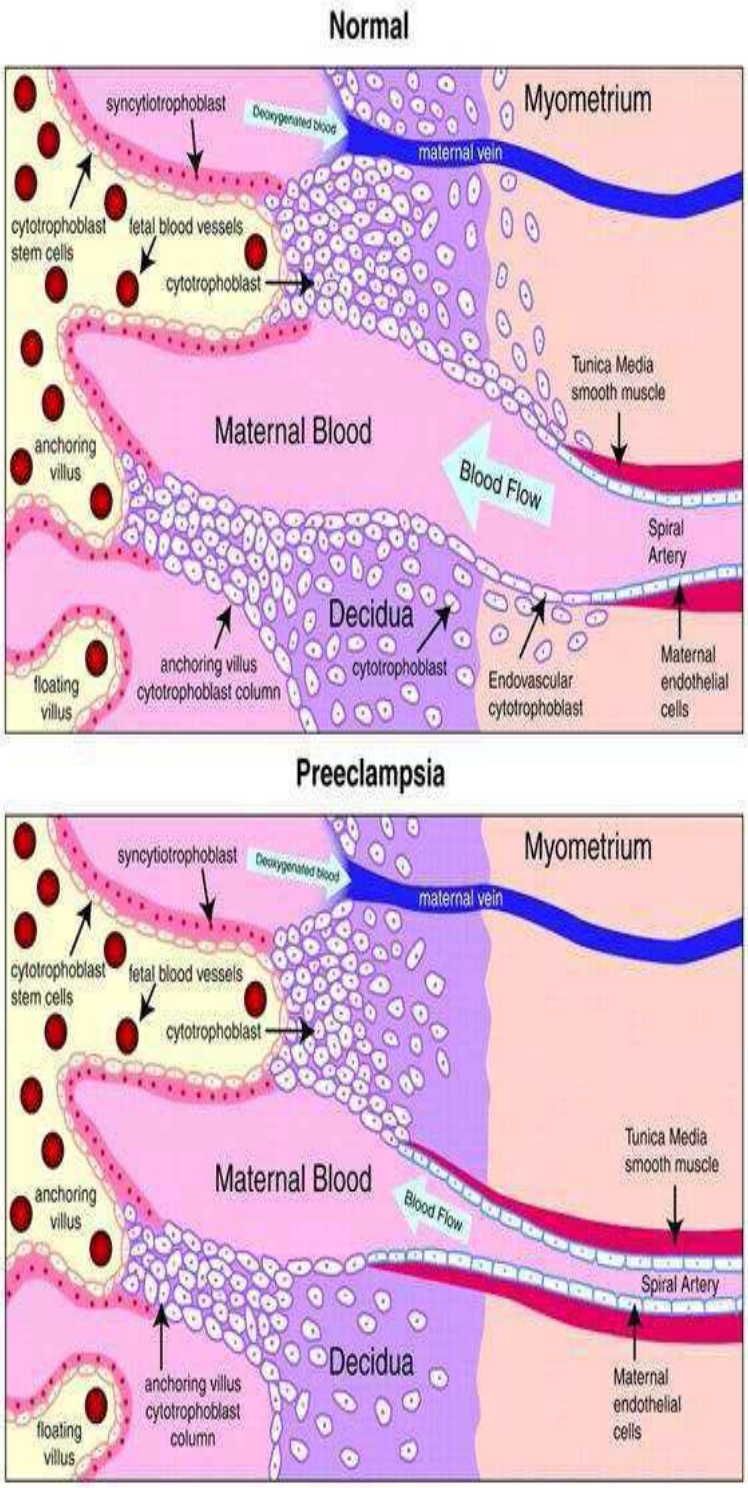
Normally the cyto trophoblasts of the developing placenta migrates through the decidua and myometrium & to invade the tunica media of the spiral

arteries which supply blood to the fetus. So these changes leads to the transformation of small muscular arterioles to large low resistence vessels.these changes occur at the end of first trimester and completed by 18 - 20 weeks of gestation.

But in pre eclampsia , cyto trophoblasts fails to penetrate the myometrial segment. So, the spiral arteries remains narrow and results in the hypoperfusion of the placenta which is the important component in pre eclampsia pathogenesis. This placental ischemia causes maternal endothelial dysfunction.

In the year 1980, dewolf and coworkers examined the arterioles from the placental implantation site using electron microscopy. They found that in ealy stages there is damage of endothelial cells, accumulation of lipids in the myointimal cells resulting in narrowed lumen.

Abnormal Trophoblastic Invasion Of Spiral Arterioles



IMMUNOLOGICAL INTOLERANCE[17]

There was a evidence to support that pre eclampsia is immune mediated. Immunologists explained that the condition where there is abnormality of immune protective mechanism are shown to prevent the mother from rejecting fetuses. To support this , there is decrease in incidence of pre eclampsia in patients who are immunosuppressed. Starting from the early second trimester, women who are at risk of developing pre eclampsia had significantly lower number of helper T cells compared with normotensive pregnant women. This Th1/Th2 imbalance was mediated by ADENOSINE, which is found to be higher in pre eclamptic mother compared with normal healthy pregnant mother.

The placental changes in pre eclampsia have shown some similarity which is found in the rejected kidney after transplantation.

" The evidence that supports this theory is there may be loss of maternal tolerance to the paternally derived placental and fetal antigens".

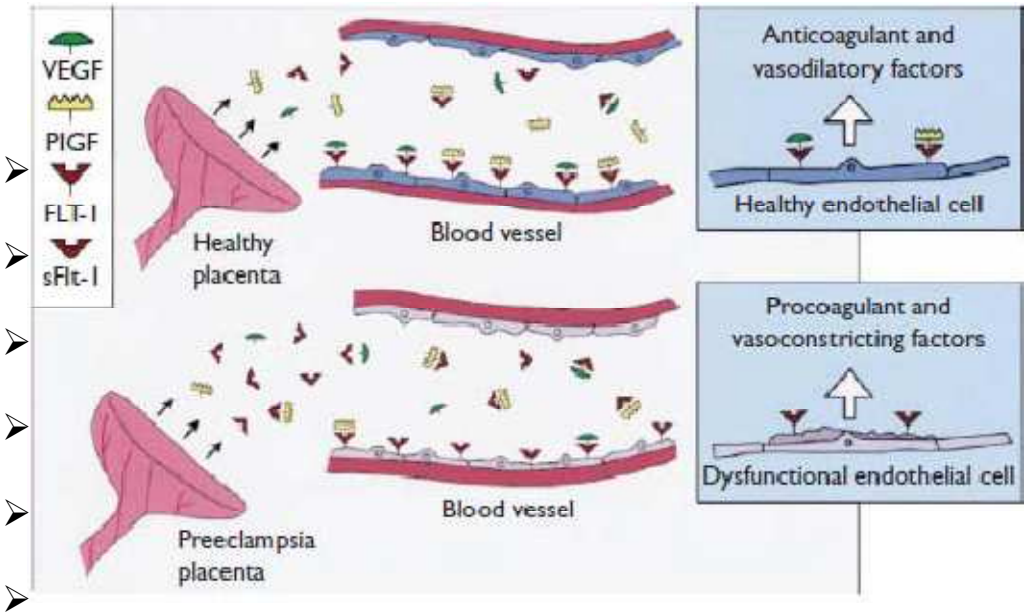
The placenta has both paternal and maternal halotypes and genetic determinants. Compared to the normal pregnant patients there is reduced level of messenger RNA for HLA-G has been noted in women with pre eclampsia.

Cytokines particularly TISSUE NECROSIS FACTOR(TNF α) and interleukin 2 (IL2) and interleukin 6(IL6) are the mediators of immune maladaptation in pre eclampsia patients.

- ***ENDOTHELIAL CELL ACTIVATION***

If the endothelium is intact, it has anticoagulant property and by releasing nitric oxide, it blunts the vascular smooth muscle response to agonist. So endothelial cell damage secretes pro coagulants and there is less nitric oxide production and there is increased sensitivity to the pressor agents.

Endothelial Cell Activation



- ***PROSTAGLANDINS***

There is decreased production of PGI_2 Prostocyclin in pre eclampsia compared with normal pregnancy. There is also an increased production of thromboxane A_2 by platelets, so the prostacyclin : thromboxane ratio decreases. This leads to increased response to vasopressor angiotensin II and finally leads to vasoconstriction

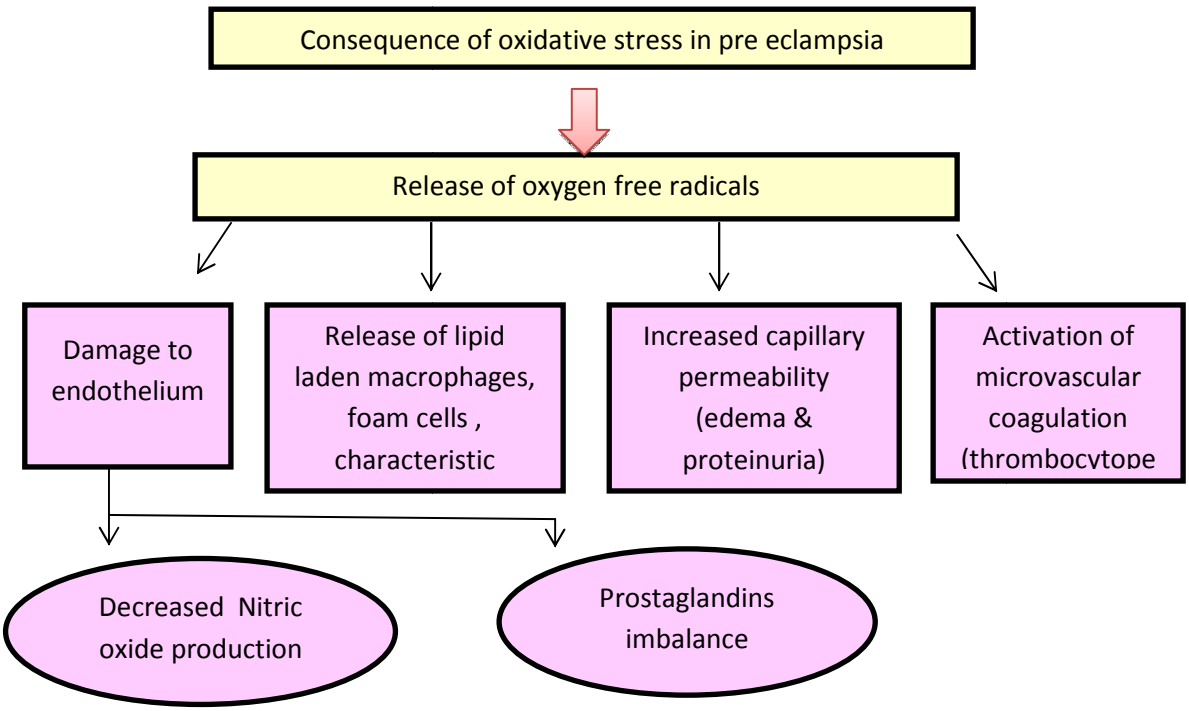
.

- ***NITRIC OXIDE***[18]

Endothelial cells produces nitric oxide from L-arginine. It is a potent vasodilator. Reduced nitric oxide synthesis in pre eclampsia increases mean arterial pressure & increases the sensitivity of vasopressor agents. The effect of nitric oxide production in pre eclampsia remains unclear.

- **OXIDATIVE STRESS**

This hypothesis states that , the pre eclampsia is due to the activated leucocytes in the maternal circulation. The decidua contains a large group of cells which on activation releases noxious agents like tumor necrosis factor-α, leukotrienes , etc which are responsible for oxidative stress in the body.



- ***ENDOTHELINS[19]***

Endothelin is a potent vasoconstrictor and it is the primary form produced by human endothelium. Endothelin levels are increased in pre eclamptic women compared with normotensive women. Some of the report shows that the magnesium sulphate decreases the endothelin I concentration.

- ***ANGIOGENIC AND ANTI ANGIOGENIC PROTEINS***

The balance between the angiogenic and anti angiogenic factors are responsible for the normal development of placenta.

In the pre eclampsia, there is increased production of antiangiogenic factors which resultsin endothelial dysfunction. Researches are currently on the use of antiangiogenic proteins in the prediction and diagnosis of pre eclampsia.

The two antiangiogenic proteins that increased in the maternal circulation are :

a. Soluble endoglin:

It is the 65 kDa molecule derived from placenta . This inhibits TGF-β isotopes from binding with endothelial receptors, which decreases the nitric oxide release from the endothelium.

b. Soluble FMS like tyrosine kinase – 1 :

It decreases the placental endothelial growth factor and vascular endothelial growth factor, which leads to the endothelial dysfunction.

Both these antiangiogenic factors begins to rise in the maternal serum before pre eclampsia develops .

Elevated level of antiangiogenic factors in second trimester is associated with increased risk of pre eclampsia .it is produced by the trophoblastic tissue , which enters in to the maternal circulation. So there is angiogenic imbalance.

- **RETENTION OF SODIUM**

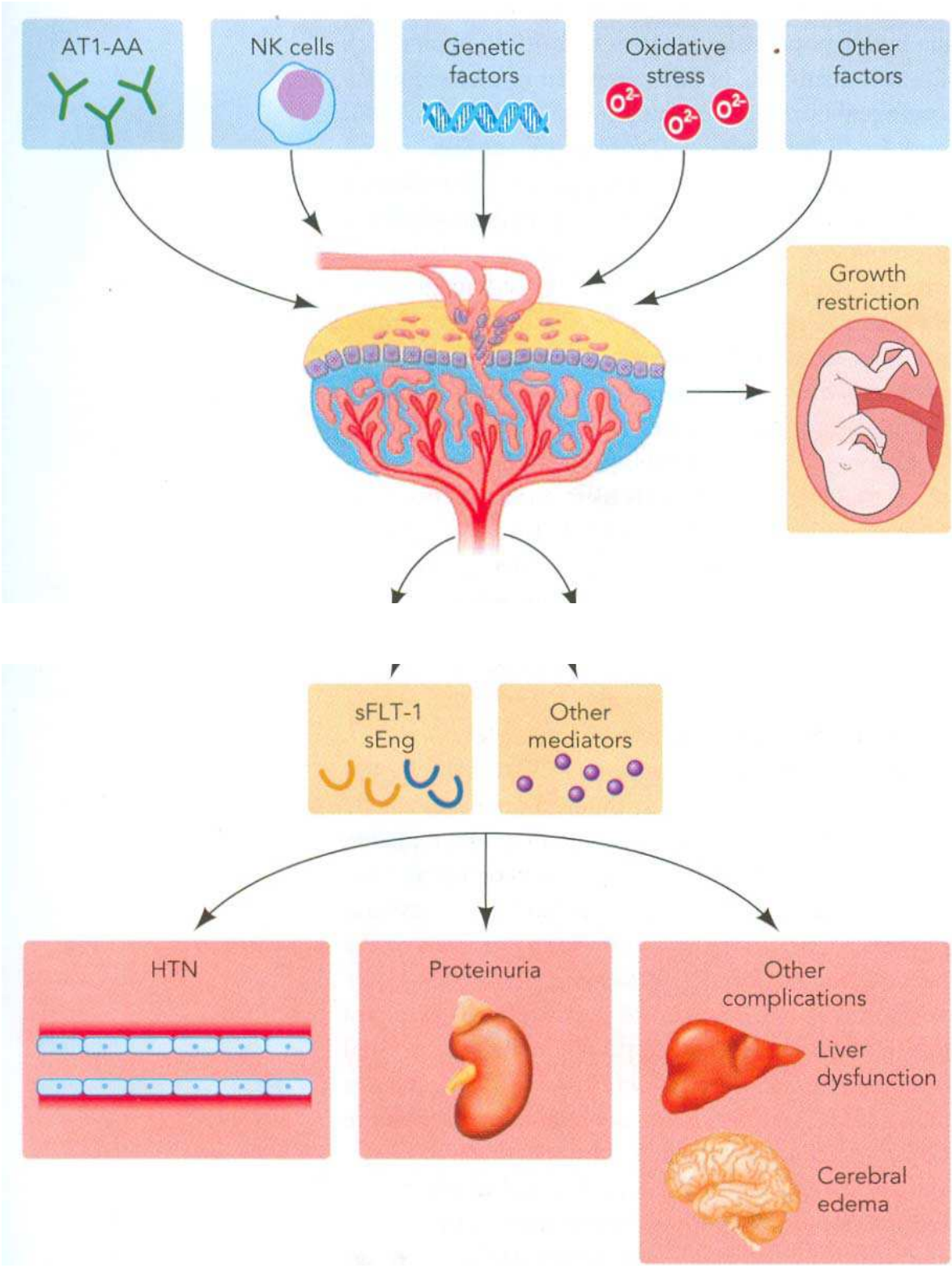
There is increased plasma volume , glomerular filtration rate and renal blood flow in normal pregnancy, but in pre eclamptic women, there is reduced plasma volume, renal blood flow and glomerular filtration rate. So there is retention of sodium occurs which increases the sensitivity of vasopressor agents in pre eclampsia.

All the signs and symptoms of pre eclampsia are well explained by response to generalised endothelial dysfunction.

1. Increased vascular permeability leads to proteinuria and edema.
2. Disturbed vascular tone of the endothelial cells leads to the hypertension.
3. Expression of pro-coagulants leads to coagulaopathy.

4. Endothelial dysfunction in the vasculature of brain, liver, kidney & placenta causes headache, seizures, epigastric pain, visual disturbances and fetal growth restriction
5. In severe pre eclampsia , angiotensin II causes vasoconstriction which leads to local hypoxia and causes haemorrhage & necrosis and other end organ damages.

Overview of pathophysiology of pre eclampsia



PATHOLOGICAL CHANGES

Pre eclampsia is a two stage disease .

- Asymptomatic stage

  Abnormal placental development during first trimester.

  ↓

  Placental insufficiency and release of placental materials in maternal circulation.

- Symptomatic stage

  Hypertension, renal involvement, proteinuria.

1. CARDIO VASCULAR SYSTEM

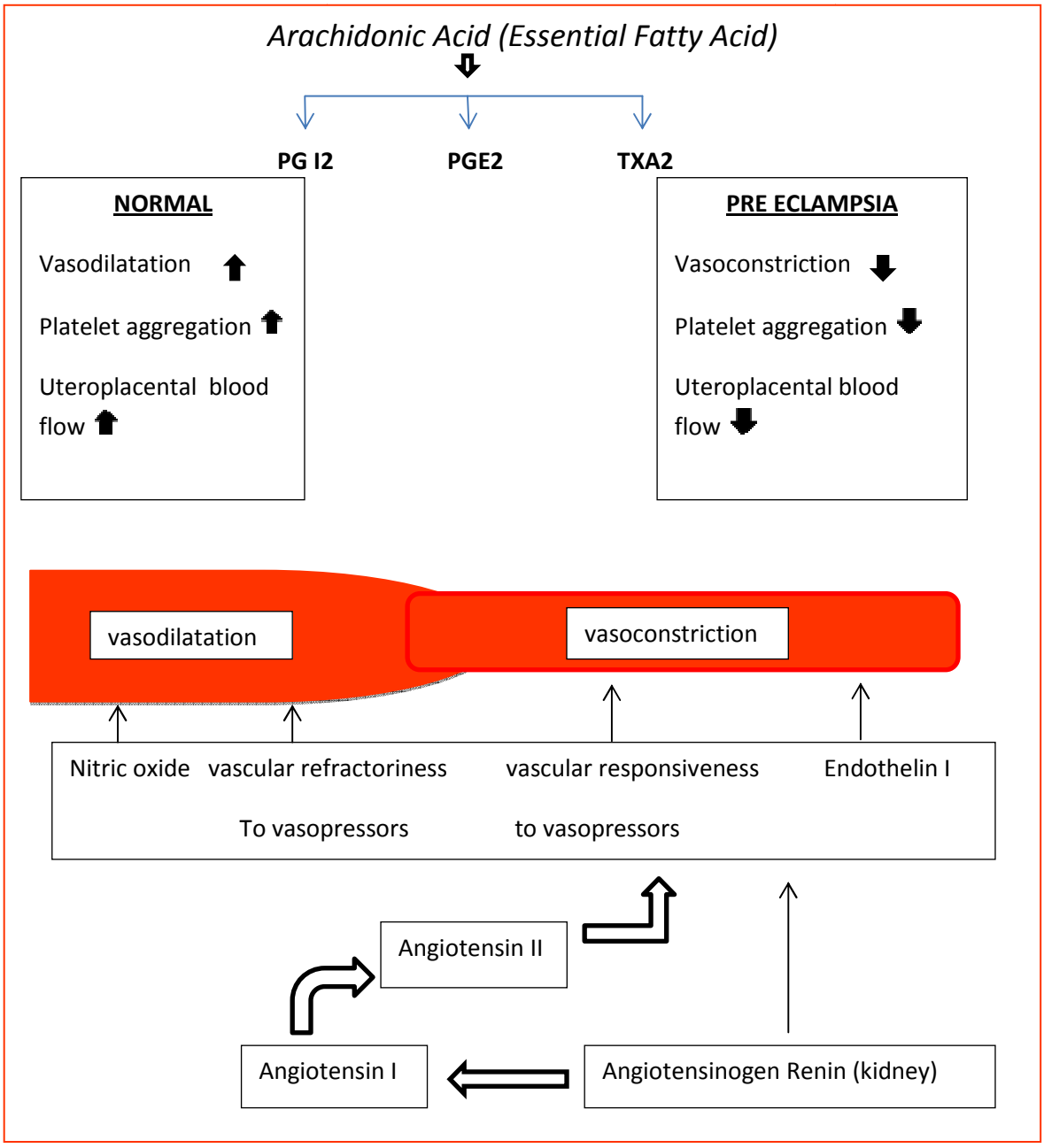
Blood pressure = cardiac output X total peripheral resistance.

Normally cardiac output is increased during pregnancy, but it rises further in the patients with pre eclampsia. Total peripheral resistance decreases during normal pregnancy whereas in gestational hypertension it increases. This is the main cause of blood pressure in gestational hypertension. Normal or hyperdynamic ventricular function is presented in these women.

In pre eclamptic women, there is an increased chance of pulmonary edema despite the normal ventricular function because of the alveolar

endothelial – epithelial leak that is compounded by decreased oncotic pressure pressure from low serum albumin concentration.

Pathophysiology of pre eclampsia chart



HEMATOLOGICAL SYSTEM

In normal pregnancy, total blood volume increases because of expansion of plasma leading to physiological anemia of pregnancy. The expansion in blood volume is reduced in gestational hypertension. Decreased regional perfusion in gestational hypertension results in the hemoconcentration.

Contraction of the intravascular space is associated with the vasospasm and subsequent hemoconcentration. Haematocrit increases with increased severity of pre eclampsia. An attempt to is made to expand the intravascular space by fluid therapy may increase the pulmonary wedge pressure and results in pulmonary edema because of capillary leak.

The main pathophysiology of pre eclampsia is the vasospasm , which results in the endothelial injury. The endothelial injury is responsible for the microangiopathic hemolysis. It results in fragmentation of red blood cells, thrombocytopenia and anemia.

It is associated with low levels of antithrombin III, high levels of fibronectin and low levels of α_2 –antiplasmin. These factors can help in the diagnosis of pre eclampsia and it differentiates from the chronic hypertension.

BLOOD AND COAGULATION

Among the haematological abnormality, thrombocytopenia is commonly identified in the women with pre eclampsia, it may be life threatening.

Activation of the platelets will lead to the endothelial dysfunction.

The coagulation system is activated by the tissue factor that is present on the endothelium. This results in widespread disseminated intravascular coagulation(DIC).

THROMBOCYTOPENIA

Thrombocytopenia has been described by stancke in the year 1922, in the patients with pre eclampsia. The platelet count is routinely examined in all gestational hypertension patients.

The intensity of thrombocytopenia depends on the duration and severity of pre eclampsia. The platelet count < 1 lakh/µL indicates severe disease. The platelet count decreases on the first day after delivery, the reaches the normal level in 4 to 5 days. Lower the platelet count , there is higher the maternal and fetal morbidity and mortality.

HELLP SYNDROME

In addition to thrombocytopenia and hemolysis, there is elevated liver enzymes level in the patients with severe pre eclampsia, it indicates hepatocellular necrosis.

COAGULATION

Following are some of the abnormalities noted in pre eclampsia

- Decreased levels of antithrombin III
- Decreased levels of protein c and s
- Decreased plasma fibrinogen level
- Increased levels of fibrin degradation products
- Increased levels of fibrino peptides A & B

ENDOCRINE SYSTEM

Angiotensin II , catecholamine and vasopressin play an important role in elevation of blood pressure and increase in vascular resistance. Vascular sensitivity to angiotensin II occurs 8 to 12 weeks prior to the onset of clinical symptoms of hypertension.

Indomethacin and aspirin are prostaglandin inhibitors decreases the vascular sensitivity to angiotensin II.

RENAL SYSTEM[20]

In pre eclampsia, there is reduced renal perfusionand glomerular filtration rate. It occurs due to increased resistance of renal afferent arterioles. Glomerular endotheliosis occurs which block the filtration barrier. Sodium concentration in urine is elevated. Fractional excretion of sodium urine osmolality and urine plasma creatinine ratio is an indication of pre renal involvement.

Serum uric acid concentration is elevated in pre eclampsia. It is due to the reduction in glomerular filtration rate and increased tubular reabsorption. In pre eclampsia there is decreased urinary excretion of calcium occurs ,therefore Hypocalciuria occurs.

RENIN – ANGIOTENSIN – ALDOSTERONE SYSTEM

It is responsible for the maintainence of blood pressure, sodium and blood volume status. In normal pregnancy, plasma renin concentration and its activity, angiotensinII and aldosterone levels are increased. Normally pregnant women have reduced refractoriness to angiotensin II effects.

But in patients with pre eclampsia, there is loss of refactoriness to angiotensin II effects. This is demonstrated as early as 18 to 22 weeks of gestation by pressor response to infused angiotensin II.

LIVER

The commonly found pathological lesion in liver is periportal haemorrhagic necrosis in the periphery of liver.

In the following circumstances, liver involvement is clinically significantSymptoms manifest as right upper epigastric pain and tenderness associated with elevation of liver enzymes alanine transferase and aspartate transferase usually seen with severe disease.

Elevation of liver enzymes without symptoms are considered as markers of severe pre eclampsia. They ususally normalize within 3 days of delivery.

Areas of infarction in liver form hepatic haemorrhage which in turn extend to form subcapsular hematoma. It is diagnosed using CT or MRI. Sometimes preeclampsia is confused with acute fatty liver of pregnancy, because it is also associated with hypertension, thrombocytopenia and elevated liver enzymes.

The incidence of subcapsular liver hematoma is 1.6 percentage.

BRAIN PATHOLOGY

The brain involvement in pre eclampsia was first described from the autopsy specimens. But CT, MRI and DOPPLER studies gives much more important information of cerebrovascular system.

ANATOMICAL LESIONS

Intracerebral haemorrhage is seen in 60 percentage of eclamptic women and it is fatal in 30% of eclamptic women.cortical and subcortical petechial haemorrhage areother lesions found in the autopsy of eclamptic women.

Some of the other lesions noted are haemorrhage in pons or basal ganglia, sub cortical edema, multiple non haemorrhagic areas of softening are seen. The microscopic appearance of vascular lesions consists of perivascular microinfarcts and haemorrhages and fibrinoid necrosis of arteriolar walls.

CEREBROVASCULAR PATHOPHYSIOLOGY

There are two theories to explain the cerebral involvement in women with eclampsia.

- The first theory explains that there is vasospasm in the cerebrovascular system. This is based on angiographic images of diffuse or focal segmental narrowing of vessels. So the diminished cerebral blood flow results in ischemia, infarction and edema.
- The second theory is postulated that if there is sudden elevation of blood pressure it may exceed the normal auto regulatory capacity.

There is disruption in the end capillary pressure which results in Vasogenic edema because of increased hydrostatic pressure, extravastation of plasma and red cells through the tight junctional opening.

CEREBRAL BLOOD FLOW

Autoregulation is defined as the cerebral blood flowwhich remains constant though there is a change in the cerebral blood flow pressure. Eclamptic seizures explains that auto regulation is disrupted during pregnancy with pre eclampsia.

MRI shows that the cerebral blood flow during pregnancy is similar to that of non- pregnant levels until it decreases by 20 percent by late trimester.

CLINICAL SYMPTOMS

1. Headache

   Thought to be as a result of cerebral hyper perfusion, 50 to 75 percentage of women had headache and 20 to 30 percentage have visual symptoms which proceed on to convulsions.

2. Convulsions
3. Blindness

   It is rare in pre eclamptic women, but complicates eclamptic convulsion.Generalised cerebral edema occur which may cause changes in the mental status.

VISUAL CHANGES

Diplopia , blurring of vision and scotoma manifest in severe pre eclampsia and eclampsia. Blindness is less common and it is reversible. These visual changes arise from the retina, visual cortex of occipital lobe and lateral geniculate nuclei.

Occipital blindness is known as amaurosis, (in greek – dimming). Retinal lesions caused by retinal ischemia or infarction results in blindness known as purstcher retinopathy. Retinal detachment also cause altered vision. Occasionally it accompanies with cortical edema. Surgical treatment is not indicated and the prognosis is ususally good and vision returns to normal within a week.

UTEROPLACENTAL PERFUSION

Vasospasm results in reduced uteroplacental perfusion which plays a important role in the pathogenesis of pre eclampsia. Previously studies were done to access the uteroplacental perfusion by peak systolic : diastolic velocity ratios from uterine and umblical arteries in women with pre eclampsia.

CALCIUM

“pregnancy is a state of calcium loss in which mother must provide 25 to 30 gm of calcium that makes up the fetal skeleton at birth”

During the third trimester of pregnancy, fetal calcium demand increases because during this period fetal skeleton undergoes mineralisation. This demand constitutes more homeoststic stress for maternal calcium metabolism, but the maternal response to this demand have not been studied .

Calcium is the most prevalent cation in the body and it is fifth most common element. An average human body approximately contains 1 kg of calcium (24.95mol). 99% of the body’s calcium present in the skeleton , predominantly as the extracellular crystals of unknown structure.

Normal calcium concentration in plasma is approximately 9.5mg/dl(2.38mmol/L).

Calcium exists in three states

- 50% is free ionised calcium
- 40% is bound to plasma protein.
  - 80% of which is bound with albumin
  - 20% of which is bound with globulin.
- 10% is complexed with small ions.

Biologically active form of calcium is free calcium and it is regulated by the parathormone (PTH) and 1,25 dihydroxycholecalciferol.

Calcium is classified physiologically as intracellular or extracellular calcium. Intracellular calcium plays an important role in physiologic functions such as hormone secretion , glycogen metabolism, muscle contraction and cell division.

Extracellular calcium provides calcium ions for the bone mineralisation, coagulation of blood and plasma membrane potential. It influences permeability and excitability of plasma membrane.

When free serum calcium decreases there is increased neuromuscular excitability and tetany and increased serum calcium reduces neuromuscular excitability.

HORMONAL REGULATION OF CALCIUM METABOLISM

1. Parathyroid hormone[21]

Low levels of serum calcium stimulate the secretion of PTH and increased levels of serum calcium inhibiting the effect of PTH.

There is an increased secretion of parathyroid hormone during pregnancy. It indicates that there is maternal adjustment to the expanding extracellular fluid volume and loss of calcium via placental transfer and urinary excretion.

" some studies suggest that the increase in PTH levels are limited to the last trimester and it is double the time of non pregnant values, whereas some studies proposed that there is gradual increase in the PTH level of about 30 % to 50% at term."

2. Calcitonin[22]

It is secreted by parafollicular cells (c-cells) of the thyroid gland. It is a 32- aminoacid peptide. Increase in plasma calcium concentration , stimulate the secretion of calcitonin. It is also secreted in response to gastrin , secretin and glucagon.

- It decreases calcium reabsorption from the kidney.
- It decreases uptake from the intestines.
- It increases deposition in bones.***

"during pregnancy, calcitonin secretion increases, thereby it protect the pregnant women skeleton from parathyroid hormone induced resorption, but the PTH's action in the kidney and gut is never affected.

3. Vitamin D

It is taken in a preformed state or synthesized in the skin by the ultraviolet light action.

Some of the studies shown that altered calcium metabolism plays a role in the pathophysiology of pre eclampsia. So researches are focussing on

prevention of pre eclampsia rather than the treatment. Among the prevention modalities, calcium and magnesium supplementation is included.

Various studies shown that there is relationship between the changes in concentration of various chemicals in mother's serum and aggrevation of hypertensive complication. Significantly, the reduction is serum magnesium and calciumconcentration was noted in pre eclamptic mothers[23,24].

Severe alteration in calcium metabolism have been identified in the pathogenesis of pre eclampsia. Some of the metabolic abnormalities include,

- Decrease in urinary calcium excretion
- Decrease in serum 1,25-dihydroxycholecalciferol concentration.
- Decrease in serum ionized calcium concentration.

Studies have shown that in pre eclampsia , there is an increased intracellular calcium in erythrocytes and platelets which results in vasoconstriction.

Indirectly calcium affects smooth muscle cell contractility by influencing the production of vasoactive agents such as prostacyclin, nitric oxide or angiotensin (renin – angiotensin pathway)[25].

Renal excretion of calcium and phosphate increases during normal pregnancy. Excretion of calcium in normal pregnancy is 350- 650 mg/day compared with 100- 250 mg/ day in non pregnantal women[26].

For each trimester, renal excretion usually increases, reaches maximum levels during 3rd trimester.Pre eclampsia is associated with hypocalciuria and many studies reporting that there is no such correlation.

Hypocalciuria results in significant increase in serum calcium levels, which activate phospholipase A_2 to stimulate prostaglandin synthesis. One of the study report that daily intake of 2000 mg calcium significantly lowers the incidence of toxemia[27].

MEASUREMENTS OF TOTAL CALCIUM

The methods routinely used for the measurements of calcium in clinical laboratories are

- Photometric method
- Ion selective electrodes method.
- Atomic absorption photometry method.

In 2004, college of American pathologist comprehensive chemistry survey, revealed that 79% of clinical laboratories used photometric methods and 20% used ion selective electrode method.

The reference intervals for total and free calcium in serum and plasma of adults:

- Total calcium - 8.6 to 10.2 mg/dl
- Free calcium (ionized) – 4.6 to 5.3 mg/dl

URIC ACID

In humans, uric acid (2,6,8 – trihydroxy purine) is the major product of catabolism of purine nucleosides, adenosine and guanosine. Purines are formed from the catabolism of dietary nucleic acids and then converted to uric acid directly. Degradation of endogenous nucleic acid was excreted as uric acid.

Dietary source of uric acid contribute around 300 mg and the rate of synthesis of uric acid is approximately 400 mg.

The starting material for purine nucleotide synthesis is ribose 5 phosphate, which is formed in the hexose monophosphate shunt pathway of carbohydrate metabolism.

It reacts with ATP and form phosphoribosyl pyrophosphate(PRPP). It regulates denovo purine synthesis. Glutamine transfers its amide nitrogen to phosphoribosyl pyrophosphate and produce 5 phosphoribosyl amine. The activity of the enzyme PRPP amido transferase is controlled by feedback inhibition of nucleotides(IMP, AMP & GMP). This reaction is the committed step in the purine nucleotide synthesis.

Inoline monophosphate is the first purine nucleotide formed by ring closure. Adenosine and guanosine monophosphates are derived from IMP through enzymatically mediated interconversions.

CATABOLISM OF PURINES

It begins with removal of theirs ribose linked phosphate, a process catalysed by purine 5 nucleotidase. Hypoxanthine and guanine are formed by the removal of ribose moiety of inosine and guanosine by the action of purine nucleotide phosphorylase.xanthine oxide converts this xanthine to uric acid.

In general , uric acid stimulates the release of IL-6, IL-1β, TNFα and monocyte chemoattractant protein. It is an antioxidant.

The association between the pre eclampsia and increased serum uric acid concentration was first reported in the year 1917.

"Hyperuricemia in pre eclapmsia is evident from 1st trimester itself". Elevated serum uric acid level is associated with adverse fetal outcome in hypertensive pregnancies[28].

Uric acid is not only a marker for the severity of disease but it is directly involved in the pathogenesis of pre eclampsia . Uric acid causes endothelial dysfunction inflammation and oxidative stress[29].

Severity of pre eclampsia is directly proportional to uric acid level. Purine metabolism by xanthine oxidase is responsible for production of uric acid

along with production of free radical super oxide(O_2^-), which is involved in the oxidative stress. The stimuli responsible for the xanthine oxidase activity remains unclear.

Hyperuricemia was noted in 75% of women with clinically diagnosed pre eclampsia and 16% of women with gestational hypertension without proteinuria. Pregnancy induced hypertension with hyperuricemia was associated with increased adverse neonatal and maternal outcome.

Increased uric acid concentration even in the absence of proteinuria may cause pre term birth and growth restriction. It is elevated in the serum as early as 10 weeks of gestation[30].

Through the organic anion, Uric acid enters smooth muscle cells and activates intracellular nuclear transcription factor and nitrogen activated protein kinase. It also stimulates the production of thromboaxane, angiotensin II and c - reactive protein.

The placental vessels has no autonomic innervation, it entirely depends on the locally produced circulating substance for hemodynamic control.

Uric acid reduces the eNos activity so that it decreases the nitric oxide production and increases the generation of potent vasoconstrictor thromboxane[31].

Uric acid level is not uniformally elevated in women with pre eclampsia but it is increased in a subset of pre eclampstic women , they are at increased risk of maternal and fetal morbidities.

Reference values

- Male – 3.5 to 7.2 mg/dl
- Female – 2.6 to 6.0 mg/dl

During pregnancy:

Normally uric acid concentration decreased during 1st trimester until 24 weeks of gestation , then it begin to increase and exceed the value of non pregnant women.

Due to the effect of estrogen, increased glomerular filtration rate and increased blood volume there is a fall in the uric acid concentration during early trimester. But in case of pre eclampsia, there is hypovolemia which increases uric acid reabsorption which increase serum uric acid level.

- 1st trimester - 2.0 to 4.3 mg/dl(Williams 23rd edition)
- 2nd trimester – 2.4 to 4.9 mg/ dl
- 3rd trimester - 3.1 to 6.3 mg/dl

ALBUMIN – CREATININE RATIO

Proteinuria (albuminuria) is considered as an independent risk factor for renal disease and cardiovascular disease and as a predictor of end organ damage.

Detection of increase in protein excretion have both diagnostic and prognostic value in the initial detection and confirmation of renal disease and also helpful in assessing the progression of disease and the effectiveness of therapy.

An increase in protein excretion was used in the early detection of certain specific conditions such as pre eclampsia , diabetic nephropathy and nephrotoxicity due to drugs.

Proteinuria gradually increases throughout pregnancy and it is the result of selective glomerular filtration.

Normally, levels of 5mg/100ml in the first and second trimester and 10 mg/100ml in the third trimester are normal. It may reach upto 300mg/day in a normal pregnancy in the third trimester. Values in excess of 15mg/100ml or 300mg/day are associated with pre eclampsia or underlying renal disease[32].

Dipstick proteinuria was used as semiquantitative method, it is equivalent to 300mg/L, 2+ to 1g/L and 3+ to 3g/L (RCOG).

Pre eclampsia is considered as severe if there is massive proteinuria of >5gm/day. It can be measured by quantification , either the total protein or of urinary albumin. So the increase in total proteins or albumin excretion is considered as aggravation of pre eclampsia.

" The present gold standard method for quantification of excreted proteins is by 24 hrs urine collection[33]"

The difficulties of 24 hour urine collection are well recognized however this test is unreliable in one third of cases. It is also a time consuming test. It also prolongs the hospital stay. So in our practice a rapid test may be needed. Therefore, detection of albumin in a single random urine sample may be an alternative to timed urine collections.

The excretion of protein and creatinine was reasonably constant throughout the day. When the glomerular filtration was stable some of the studies proposed that the measurement of protein to creatinine in urine samples collected over short time periods.

" The Australian society for the study of hypertension in pregnancy and the international society for the study of hypertension in pregnancy have proposed the use of urinary spot protein- creatinine ratio as an alternative to the 24 hours urinary collection[34]".

COMPLICATIONS

- Maternal
  - Central nervous system
    - Eclampsia
    - Cerebrovascular accident
      - due to intracerebral haemorrhage or occasionally intracranial aneurysmal rupture.
    - Retinal detachment
    - Cortical blindness
  - Respiratory system
    - Pulmonary edema with or without left ventricular failure

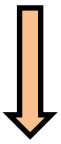
      It occurs due to excessive accumulation of fluid in the interstitial and alveolar spaces of lung. It develops in 2.9% of pregnancies complicated by pre eclampsia.
    - Acute respiratory distress syndrome
  - Renal system
    - Renal cortical necrosis
    - Renal tubular necrosis
    - Renal failure -It is characterised by marked reduction in the glomerular filtration which leads to increased retention of urea, electrolytes and acid base abnormalities.

- Liver
  - HELLP syndrome

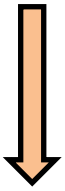
    It is associated with high maternal and fetal mortality.
  - Hepatic rupture[35]

    It is one of the most severe consequences of pre eclampsia. It occurs more commonly in the elderly women in their first pregnancy. The mechanism involved is

Endothelial dysfunction + intravascular fibrin deposits

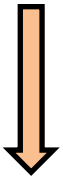


Hepatic sinusoidal obstruction



Increase in intrahepatic vascular congestion and pressure and

Distortion of Glisson's capsule



Development of subcapsular hepatic hematoma and liver rupture

- Fatty liver

  It is a rare disorder. It was first described by Sheehan in the year 1940 under the term obstetric yellow atrophy. The currently accepted pathologic hallmark of the disease is “microvesicular hepatic steatosis”.

- Haematological - Disseminated intravascular coagulation (DIC)

  It is characterised by a increase in fibrinolysis and fibrin formation which leads to consumption of clotting factors, presenting as bleeding diathesis. Severe pre eclampsia was the most common cause of disseminated intravascular coagulation.

- Placenta – abruption placenta
- Side effects of drug therapy.

➢ Fetal[36]

“ Pre eclampsia is considered to be a maternal disorder in which the fetus is an incidental participant, but from the fetus point of view , it is a fetal disorder and mother is an incidental participant.”

In congenitally normal singletons, pre eclampsia is the major cause of intra uterine growth retardation. It indicates a feature of early onsetsevere

disease. Because of diminished utero-placental blood flow, there is anoxia which leads to liberation of thromboplastic substances from the placenta which initiates intravascular coagulation.

There are many types of lesions which are found in normal placenta and are more extensive in case of pre eclampsia which includes

- Increased syncytial knots
- Increased number of true infarcts.
- Increased lose of syncytium
- Proliferation of cytotrophoblast, villous necrosis.
- Acute fibrinoid degeneration of maternal decidual arteries.

As a result of this, there is

- ✓ Increased secretion of chorionic gonadotropin
- ✓ Increased secretion of steroid hormones
- ✓ Deterioration of acute transport mechanism of vital aminoacids .

All of the above factors contributes to fetal hypoxia and IUGR of fetus.

- ✓ Intra uterine fetal growth restriction(IUGR)
    - Depends on the duration of hyper tension and the degree of proteinuria.
    - Antepartum and intrapartum asphyxia.
        - reduced placental blood flow.

- Maternal hypoxia (due to eclampsia or excess sedatives or anticonvulsants).

- Intrauterine death (IUD)
- Prematurity – it is more likely to be iatrogenic in pre eclampsia
- Fetal side effects of anti hyper tensive therapy

HELLP syndrome

In the year 1982, it was first coined by Weinstein. It comprises of

- **H**emolysis
- **E**levated **L**iver enzymes
- **L**ow Platelet count

Incidence

- 0.2 to 0.6 percentage of all pregnancy
- 10 percentage of pregnancy complicated by severe pre eclampsia.

Clinical features : Nausea , vomiting, epigastric pain.

Criteria for diagnosis of HELLP syndrome

- Hemolysis
  - Abnormal peripheral smear – burr cells, schistocytes.
  - Bilirubin >1.2 mg/dl
  - Lactate dehydrogenase >600 u/L

- Low serum haptaglobin

- Elevated liver enzymes
  - SGOT - >70 U/L
  - LDH - >600 U/L
- Low platelets - <1 lakh / mm^3.
- **Differential diagnosis**
  - Cholestasis of pregnancy
  - Acute fatty liver of pregnancy
  - Viral hepatitis
  - Haemolytic uremic syndrome.
  - Thrombotic thrombocytopenic purpura.

Management

Termination of pregnancy is considered according to the gestational age severity of condition and favourability of cervix. Prophylactic anti convulsant and anti hypertensive management are administered as indicated.

The platelet count and lactate dehydrogenase levels comes to normal by 72 hours after delivery. So they are the best markers to follow the disease progression. There is increased risk of 20 % of developing gestational hypertension in subsequent pregnancy in the women with prior history of HELLP syndrome.

ECLAMPSIA

Pre eclampsia often proceeds the onset of eclamptic convulsions. It is a preventable disease. It is more common in primi. It is defined as

> " development of generalised tonic clonic seizures/ coma in a pre eclamptic women in the absence other neurological conditions."

It is mostly associated with hypertension and proteinuria.

Classification

Eclampsia is one of the major cause of the morbidity and mortality in th pregnant women. It is classified into

- ✓ Antepartum eclampsia(38 %to 53%)
- ✓ Intrapartum eclampsia(18 % to 36%)
- ✓ Postpartum eclampsia(11% to 44%)

It is more common in last trimester. Rarely it occurs before 20 weeks in cases of

- ✓ Molar pregnancy
- ✓ Multiple pregnancy
- ✓ Antiphospholipid antibody syndrome.

Incidence

In developed countries, 1 in 2000 deliveries are complicated by eclampsia. In developing countries, 1 in 100 to 1 in 1700 cases are complicated by eclampsia. But this incidence has now fallen dramatically because of early detection and treatment.

Warning signs

- Persistent headache
- Visual disturbances
- Nausea / vomiting /epigastric pain.
- Restlessness and agitation.

Stages of eclamptic seizures

It is characterised by prodromal, tonic, clonic and recovery stages.

Prophylaxis

"The largest trial Magnesium sulphate for prevention of eclampsia (MAGPIE TRIAL collaborative group 2002), studied more than 10,000 women with severe pre eclampsia from 33 countries. Women who receiving magnesium sulphate had 58% lower risk of eclampsia than those given placebo.

Magnesium sulphate is $Mgso_4.7H_2O$ and not $Mgso_4$. It is cleared by renal excretion. Therapeutic magnesium level is maintained at 4 to 7 meq/L, 4.8 to

8.4 mg/dL or 2.0 to 3.5 mmol/L. Respiratory rate, patellar reflex and urinary output are monitored during $Mgso_4$ therapy. It is not an anti hypertensive medicine. Regardless of renal function standard loading dose is given. But the maintanence dose may be decreased according to the urinary output.

PREDICTION AND PREVENTION OF PRE ECLAMPSIA

Many attempts were made to find the early markers of impaired placenta perfusion, endothelial cell activationand dysfunction and faulty placentation. There is no valid screening test to predict pre eclampsia .

In the year 2009, conde-agudelo and associates provided the review for the tests.

Placental perfusion/ vascular resistance :

- Roll over test
- Isometric handgrip or cold pressor test
- Angiotensin II infusion
- Mid trimester mean arterial pressure
- Platelet angiotensin II binding
- Renin
- 24- hour ambulatory blood pressure monitoring
- Uterine artery
- Fetal transcranial Doppler velocimetry.

Fetal placental unit endocrine dysfunction

- Human chorionic gonadotropin(hCG)
- Alpha feto protein (AFP)
- Estriol
- Pregnancy associated protein A (PAAP A)
- Inhibin A
- Activin A
- Placental protein 13
- Corticotropin releasing hormone

Renal dysfunction

- Serum uric acid
- Microalbuminuria
- Urinary calcium or kallikrein
- Microtransferrinuria
- N-acetyl- β-glucosaminidase.

Endothelial dysfunction/ oxidant stress

- Platelet count and activation
- Fibronectin
- Endothelial adhesion molecule
- Prostaglandins &Thromboxane
- c-reactive protein & cytokines

- endothelins & neurokinins B
- VEGF, PlGF,PAI.
- Leptin & p-selectin
- Endoglin .

Miscellaneous

- Anti thrombin III
- β_2 microglobulin
- atrial natriuretic peptides.

Mean arterial pressure

MAP = diastolic blood pressure + 1/3 pulse pressure

In women, who don't have the normal fall in the blood pressure in the midtrimester, but the mean arterial pressure of 90 mm of Hg or more in the second trimester are at the risk of developing pre eclampsia.

Roll over test

If there is increase in the diastolic blood pressure of 20mm Hg or more if the woman is turned from the left lateral to the supine position , the test is considered as positive.

Angiotensin sensitivity test

In case of pre eclampsia there is loose their refactoriness to angiotensin between 28 to 32 weeks of gestation. The test is based on this above fact,that is if a pressor response occurs with <8ng/kg/min of the infused angiotensin , 90 percentage of the women was likely to develop pre eclampsia , but this test is invasive.

Uterine artery Doppler

- Non pregnant women
  - reduced diastolic flow and notching of the uterine artery
- Normal pregnancy
  - Due to the trophoblastic invasion, the notch disappears and flow increases.

" IF THERE IS PERSISTENCE OF A DIASTOLIC NOTCH IN THE UTERINE ARTERY OR INCREASED RESISTANCE AT 20 -22 WEEKS- it indicates second stage of trophoblastic invasion has not occurred"

This helps in the prediction of pre eclampsia and IUGR. In general, the uterine Doppler test is the best among all the above said test as there is no other test are truly predictive. The latest combination method in first trimester include in prediction of pre eclampsia is uterine artery Doppler along with pregnancy associated plasma protein(PAPP- A) and placental protein 13(PP13).

Methods of prevention

1. Low salt diet

Salt restriction was the earliest research efforts to prevent pre eclampsia(De snoo 1937). In 1998, knuist and collegue reported that salt restricted diet was not effective in prevention of pre eclampsia.

2. Calcium supplementation

In the 1980's(Belizan and vilar) studies were shown that patients with intake of low dietary calcium had increased the risk of pre eclampsia .

Following that there are various studies including the national institute of child health and human development (Levine and collegues 1997). Shown that unless the women has calcium deficient, calcium supplementation has no effects on reducing pre eclampsia .

3. Fish oil supplementation

Eicosapentanoic acid and alpha linoleic acid are the most common dietary source. It may prevent inflammatory mediated atherogenesis. But the randomised trials (Makrides 2006, olafsdottir 2006, olsen 2000, and their collegues)shown that there is no such benefits.

4. Antioxidants

Vitamin C &E are the two naturally occurring anti oxidants and there is reduction in the plasma level of these anti oxidants are noted in pre eclampsia.(Raijmakers and associates 2004).

Thus supplementation of anti oxidants improves the oxidative property of women who are risk of pre eclampsia. (Poston 2006, Rumbold 2006) studies revealed that the eclampsia has not reduced by the use of antioxidants.

5. Antithrombotic agents
6. Low dose aspirin

Wallenburg and associates 1986. Daily oral dosage 50 to 150 mg of aspirin inhibits thromboxane A_2 synthesis. The paris collaborative group performed a meta analysis which showed that the relative risk of pre eclampsia was reduced by 10%.

7. Low dose aspirin + heparin

High incidence of thrombotic lesion in placenta was found in the patients of severe pre eclampsia. In the year 2006, sergis and associates analyses the effect of prophylaxis with low dose aspirin with low molecular heparin in random with history of early onset pre eclampsia and low birth weight babies. They reported that there is better pregnancy outcome in patients with low dose aspirin plus low molecular heparin than those with low dose aspirin alone.

AIMS OF THE STUDY

OBJECTIVES OF THE STUDY

A study on strength of association between the changes in serum calcium, serum uric acid , urine albumin creatinine ratio and pre eclampsia and its outcome was done at Thanjavur Medical College And Hospital, Thanjavur.

The prime objectives of this study are as follows,

1. To estimate the strength of association between the changes in the serum uric acid, serum calcium, urine albumin creatinine ratio in pre eclampsia.
2. To know whether these factor in pre eclampsia influence on maternal and perinatal outcome.

METHODOLOGY

MATERIALS AND METHODOLOGY

A STUDY OF STRENGTH OF ASSOCIATION BETWEEN CHANGES IN SERUM CALCIUM , SERUM URIC ACID , URINE ALBUMIN – CREATININE RATIO AND PRE ECLAMPSIA AND ITS IMPACT ON OUTCOME.

This study was conducted in Thanjavur Medical College Hospital, Thanjavur, for a period of one year from September 2013 – August 2014.

The study groups participated voluntarily in this study and each of them gave informed consent. This study was approved by Ethical And Research Committee Of Thanjavur Medial College.

Study population

In this prospective study, total number of 100 subjects were participated , it includes 50 gestational hypertension patients as cases and 50 normotensive pregnant women as controls. Both these study groups were studied in their 28 – 32 weeks of gestation.

The study groups includes both primi and multi parous pregnant women. They were selected on the basis of simple random sampling method.

Inclusion criteria

Gestational hypertension patients and normotensive pregnant women between 28 – 32 weeks of gestation from 18 to 35 years of age.

Exclusion criteria

Prior history of chronic renal disease, diabetes mellitus, chronic hypertension, twin gestation, UTI were excluded from the study.

History regarding age, parity, socio economic status, past family and personal history was taken. General examination was done for blood pressure edema and weight gain. The investigations included serum calcium, serum uric acid and spot urinary albumin - creatinine ratio.

1. Collection of blood sample:

   Under aseptic precautions, 3ml of venous blood was collected and allowed to clot. The serum separated was then used for the estimation of calcium and uric acid using Randox Daytona auto analyser.

2. Collection of urine sample:

   The random midstream urine sample of 10 ml was collected in the sterile container without any preservatives and assayed for albumin and creatinine using Randox Daytone auto analyser.

Evaluation

These patients were regularly examined during each antenatal visits till delivery. CBC, RBS, RFT, LFT, Serum calcium, serum uric acid, urine albumin/creatinine ratio were monitored throughout the pregnancy period and its impact on the oucome was studied.

Parameter	**Method**
Serum calcium	Arzenazo III, calorimetric method
Serum uric acid	Enzyme method
Urine albumin	Immune turbidimetric method
Urine creatinine	Jaffe's method

ESTIMATION OF SERUM CALCIUM

Serum calcium was estimated by ARZENAZO – III , calorimetric method Randox auto analyser, using RANDOX KIT.

Principle

Ca^{++} + *Arsenazo III* ➔ *coloured complex*

" Arsenazo III specifically bind to calcium and and forms a coloured complex which can be measured at 650 nm"

The intensity of the coloured complex is directly proportional to the amount of calcium present in the sample.

CONTENTS	Initial concentration of the solution.
R 1 ARSENAZO III REAGENT • Arsenazo • Sodium acetate • Non reactive stabilizer	54.2 mmol/ L. Ph -5.9. Approximately 250 µ mol / L.

These reagents are stable upto the expiry date when it is stored at +15^{o}C to +25^{o}C.

Assay protocol of serum calcium

Wave length	630 nm
Reaction temperature	37^{o}C
Curet	1 cm path length
Units	Mg/dl

ESTIMATION OF SERUM URIC ACID

Serum uric acid was estimated using RANDOX KIT – UA 1614 in the Randox auto analyser by the "ENZYME METHOD ".

Principle :

" U ric acid is converted in to allantoin and hydrogen peroxide by uricase. Under the influence of peroxidase, it oxidizes 3,5 – dichloro 2 hydroxy benzene sulphonic acid and 4 amino phenazone to form red violet quinoneimine"

REAGENT COMPOSITION

Content	**Concentration in the test**
Hepes buffer	200 mmol/L, Ph – 7.55
Uricase	≥200 U/L
Peroxidase	>1000 U/L
4 amino phenazone	0.25 mmol/L
3,5 DCHBS	4mmol/ L
Standard	595 µmol/L (10 mg/dl)

Assay protocol of serum uric acid

These reagents are stable upto the expiry date when it is stored at +2^{o}C to +48^{o}C and protected from light.

Mode	**Endpoint**
Wave length	750 nm
Reaction temperature	$37^{o}C$
Cuvet	1 cm path length
Units	mg / dl

ESTIMATION OF URINARY ALBUMIN CREATININE RATIO

Urinary albumin was estimated by immune turbidimetric method.

Principle

" Turbidimetry based on the principle of agglutination reaction. It measures the reduction in the light transmitted .the urine sample is mixed with the activation buffers(R1) and anti human antibody solution and allowed to react.

The albumin present in the test specimen forms an insoluble complex which produce the turbidity, measured at the wave length of 340 nm. The resulting turbidity corresponds to the concentration of the albumin in the test specimen.

Assay protocol of urinary microalbumin

WAVE LENGTH	340 nm
REACTION TEMPERATURE	$37^{o}C$
CUVETTE	1cm path length

ESTIMATION OF URINARY CREATININE

BY JAFFE'S METHOD

Principle

"In alkaline medium, the creatinine reacts with picric acid to form a reddish yellow complex, the intensity is directly proportional to the concentration of creatinine in the specimen and can be measured at 520 nm".

Alkaline picrate reagent

4 parts of picric acid + 1 part of sodium hydroxide reagent.

The working reagent was stable for one day.

Reagent composition

Picric acid reagent	0.91 gm /dl (0.04M)
Sodium hydroxide	10 gm /dl
Stock creatinine standard	100 mg creatinine in 100 ml of 0.01 N HCL
Working creatinne standard	(10 mg/dl) prepared by dissolving 10 ml of stock standard in 0.01 N HCL to make upto 100ml.
Sulphosalicylic acid	3g/dl

RESULTS

RESULTS

The results obtained from this present study were from a total number of 100 subjects, who were categorised into

- GROUP I – Normotensive pregnant women – 50
- GROUP II – pre eclamptic pregnant women – 50

Following biochemical parameters are compared between two groups

- ✓ Serum calcium
- ✓ Serum uric acid
- ✓ Urinary albumin
- ✓ Urinary creatinine.

The following ratio is compared between two groups

- ✓ Urinary albumin / creatinine.

Statistical analysis

Data was expressed in terms of Mean ±SD. Chi square test was applied to estimate the difference between two groups. Unpaired 't' test was used to study the changes in serum uric acid , serum calcium and urinary albumin creatinine ratio.

P value >0.05 was taken as non significant.

P value <0.05 was taken as significant.

P value <0.01 was taken as highly significant.

P value <0.001 was taken as very highly significant.

AGE

The age group of the subjects was between 18 – 35 years. The mean age and standard deviation in pre eclamptic patients was 24.48 ± 2.08 years and in controls it was 23.65±2.47 years. There was no statistical difference in age between two groups.

TABLE NO :1Age distribution of cases

Age group in years	Cases number	Cases percentage
18 - 20	8	16%
21 – 25	24	48%
26 – 30	10	20%
31-35	8	16%
TOTAL	50	100%

Bar diagram 1 : Showing age distribution in pre eclampsia (cases).

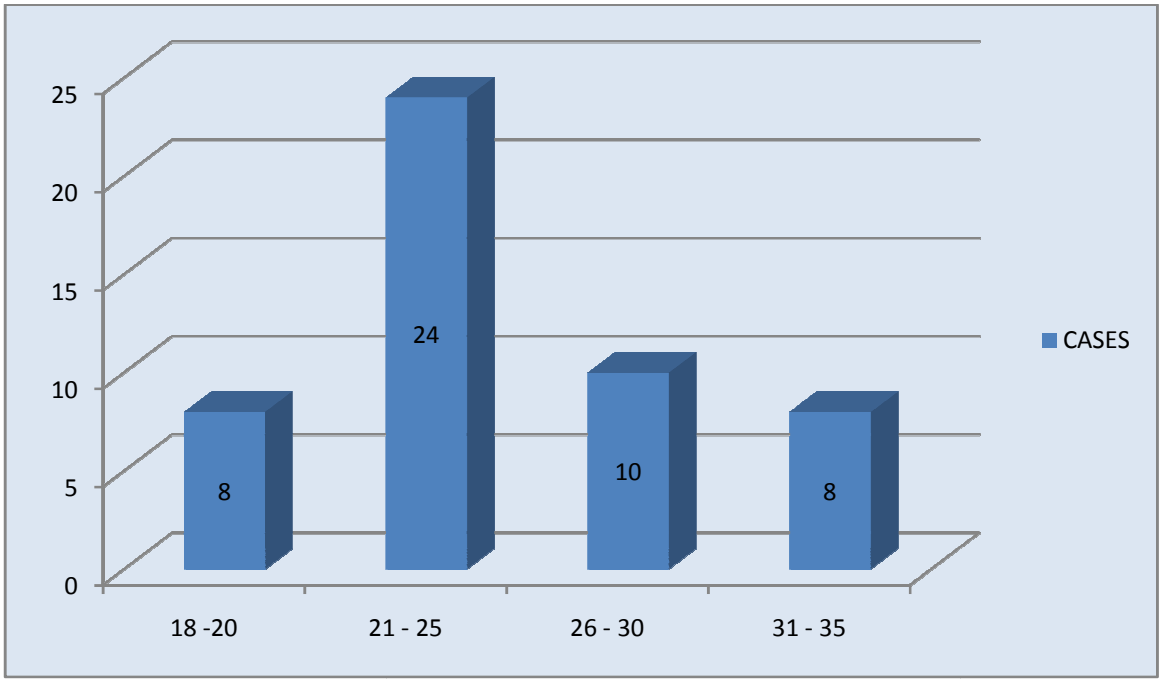
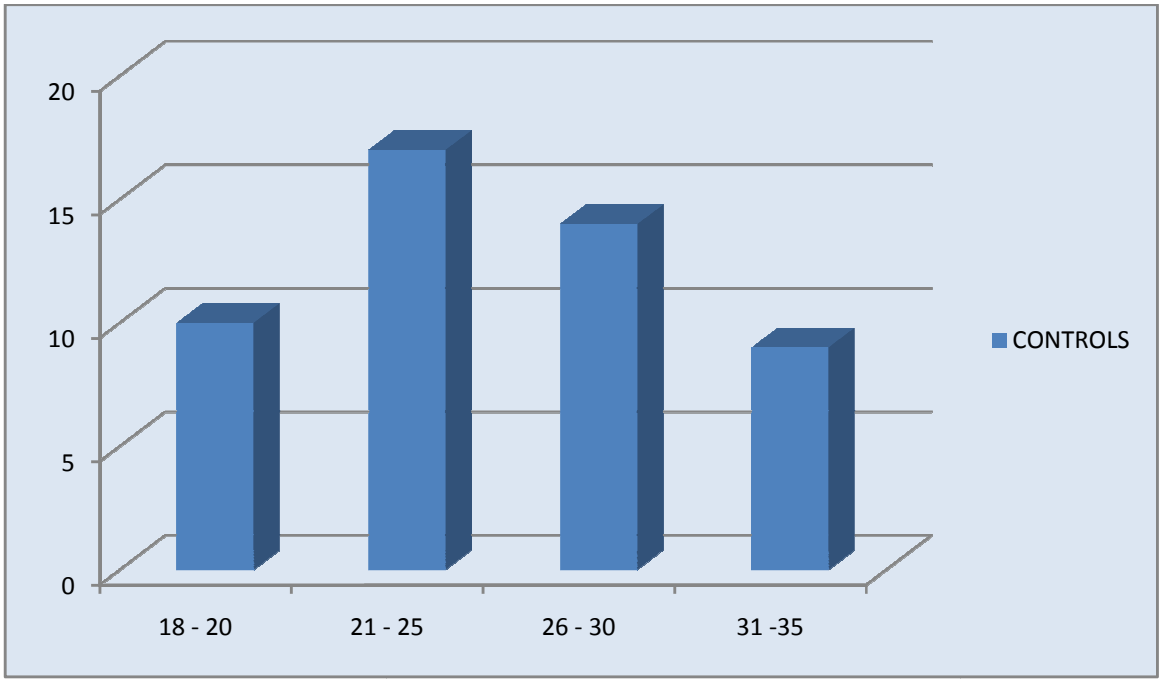


TABLE NO 2: Age distribution of controls

Age group in years	Controls number	Controls percentage
18-20	10	20%
21-25	17	34%
26-30	14	28%
31-35	9	18%
TOTAL	50	100%

Bar diagram 2: Showing age distribution in normal healthy women (controls).



PARITY

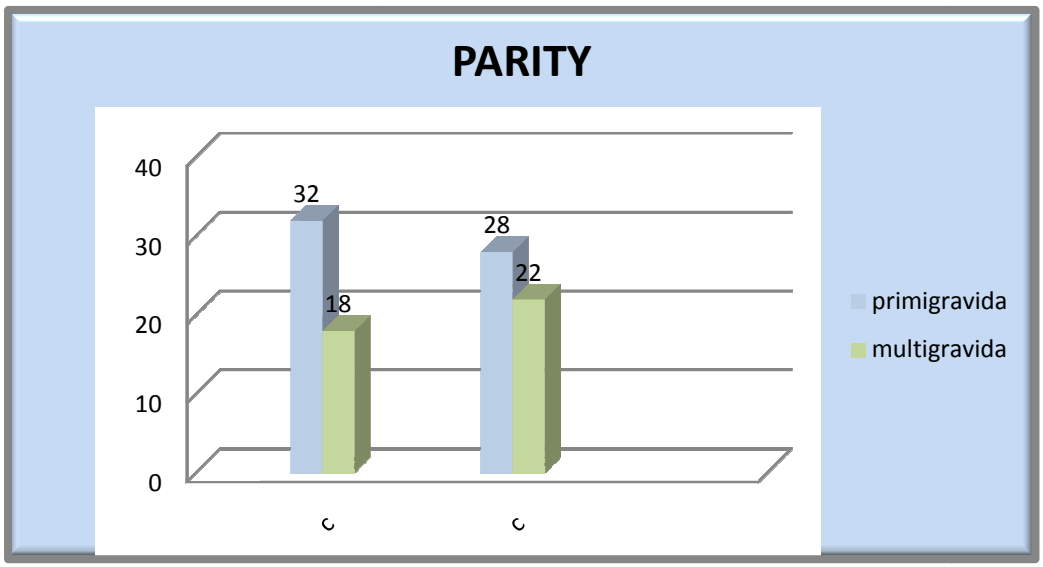
Among the pre eclamptic cases, the number of primigravida were 36 and multigravida were 14. The control group included 28 primigravida and 22 multigravida women. The cases and controls were also matched with respect to parity ($p>0.05$).

The findings show that the incidence of pre eclampsia was highest in primigravida when compared with multiparous women.

Table no 3 :Parity distribution in study groups.

Gravida	Cases	Controls
Primigravida	32	28
Multigravida	18	22
Total	50	50

Bar diagram 3 : Parity distribution in study groups



BLOOD PRESSURE

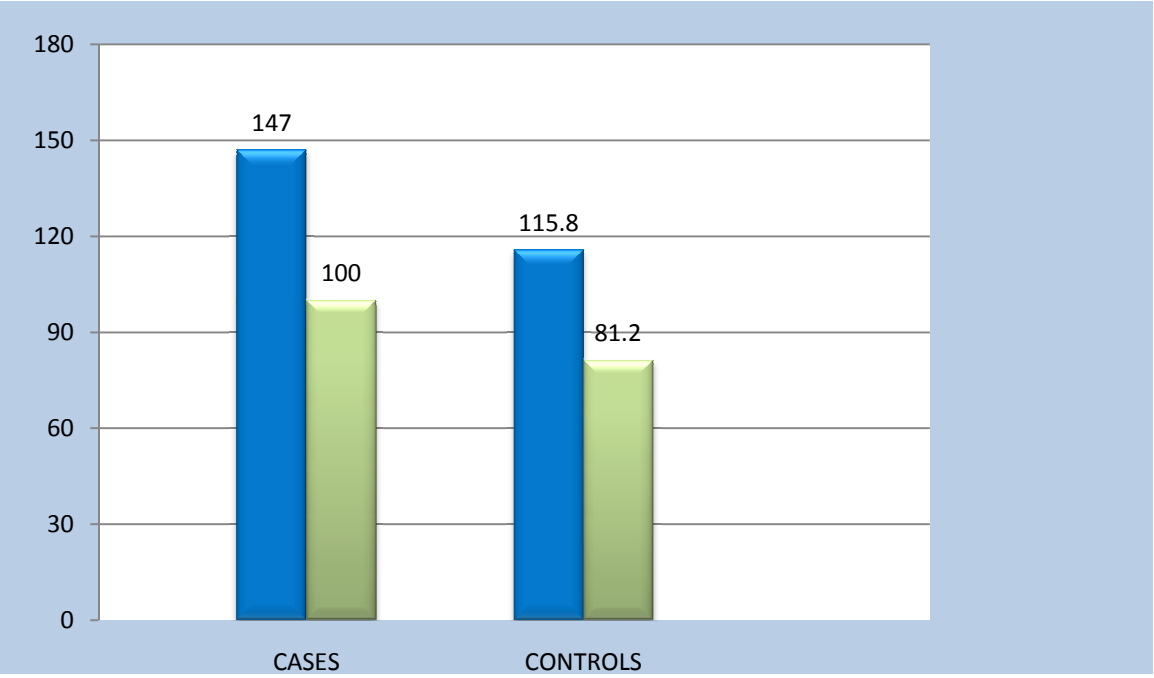
Table no 4 : showing MEAN BP ±SD of blood pressure in the study group

Group	Mean SBP with SD (mm HG)	Mean DBP with SD (mm HG)
Cases	147.34 ± 12.84	100.28 ± 8.53
Controls	115.8 ± 9.02	81.2 ± 3.83

Data are shown as Mean ± SD

There is a high statistical difference in the blood pressure both systolic and diastolic between the two groups.

Bar diagram no 4 : Showing the blood pressure values in study group



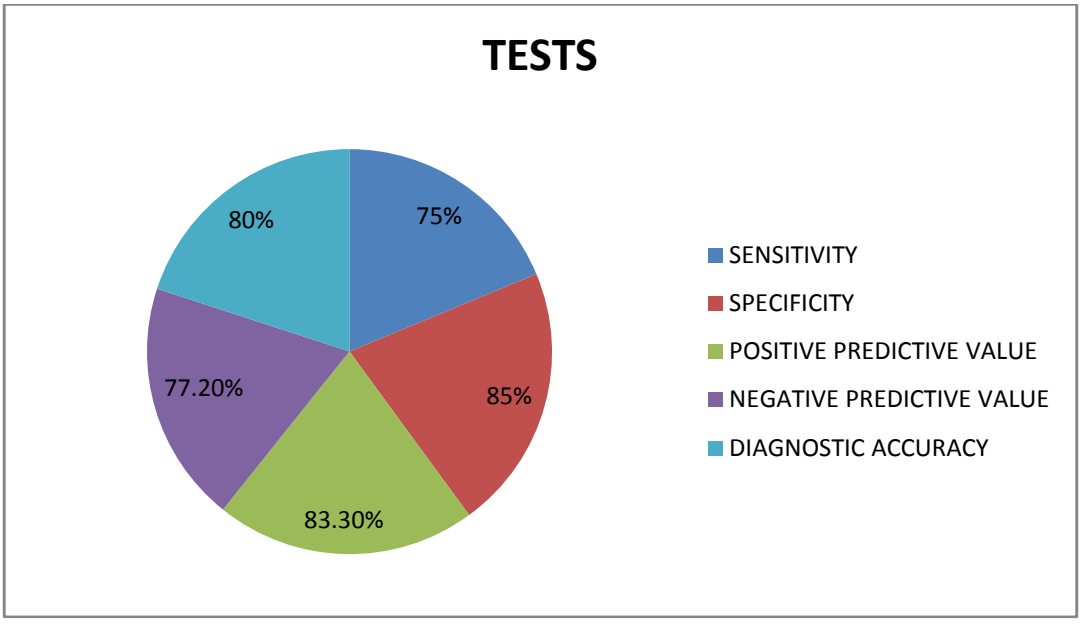
SERUM CALCIUM

Table no 5 : calcium levels in study groups

PARAMETER	CASES MEAN±SD	CONTROLS MEAN±SD	't' value	'p' value	Significance
Calcium mg/dl	8.29±0.69	9.73±0.72	10.168	<0.0001	High

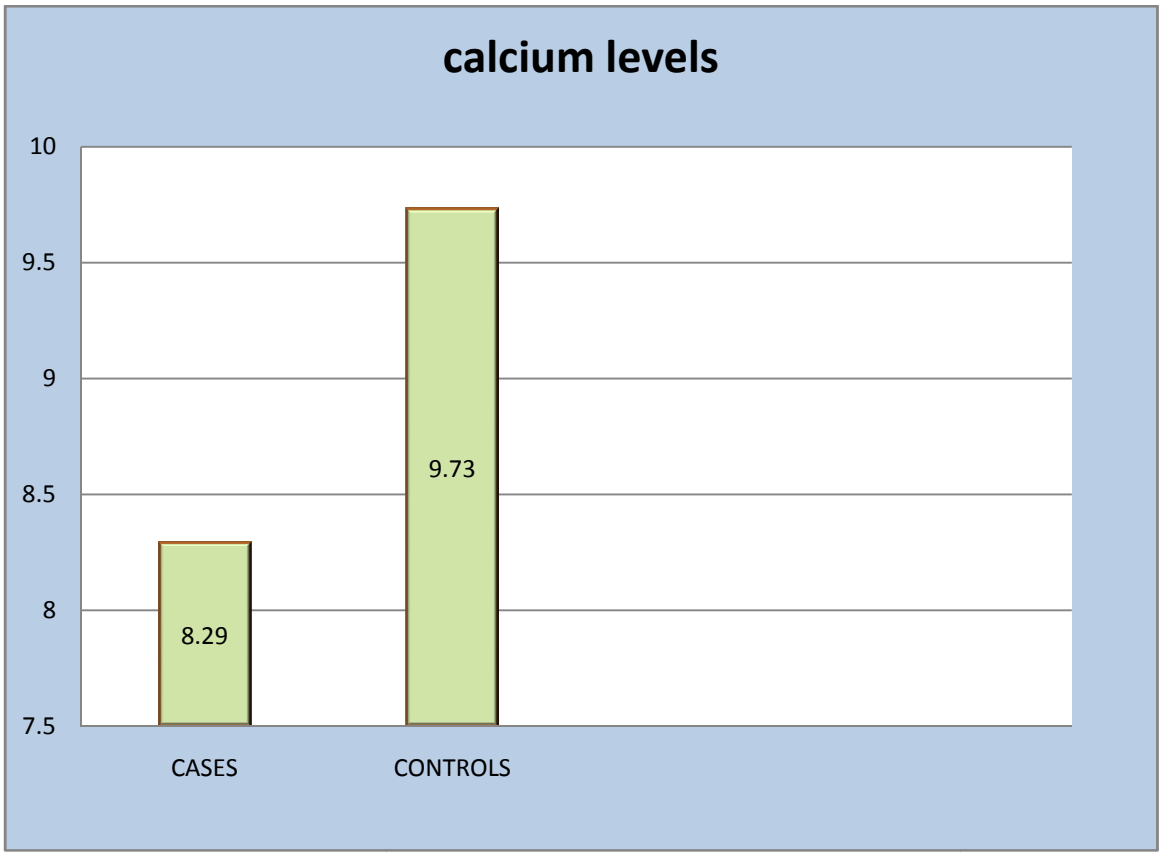
- Sensitivity = 75%
- Specificity = 85 %
- Positive Predictive Value = 83.3 %
- Negative Predictive Value = 77.2 %
- Diagnostic Accuracy = 80%

Pie chart 5 : Diagnostic value of serum calcium in study groups



The [Mean ±SD] serum calcium levels in cases was 8.29 ±0.69 mg/dl and in controls 9.73±0.72 mg/dl. There is a high stastical difference in the serum calcium levels between the two groups.

Bar diagram no 6 :Serum calcium levels in cases and controls



COMPARISON OF SERUM URIC ACID

BETWEEN CASES AND CONTROLS

Table no 6 : serum uric acid in study groups

GROUPS	**SERUM URIC ACID (mg/dl)**	
	Range	Mean ± SD
Cases	3.98 -8.61	6.7 ±1.1
Controls	2.52 – 6.24	4.26±1.03
t*	0.08	
P	0.0045 ,HS.	

*-unpaired test HS – highly significant.

The mean serum uric acid levels (mg/dl) in cases and in controls were 6.7 ±1.1 and 4.26±1.03 respectively and it was highly significant (p- 0.0045).

Bar diagram no 7 : serum uric acid values in study groups

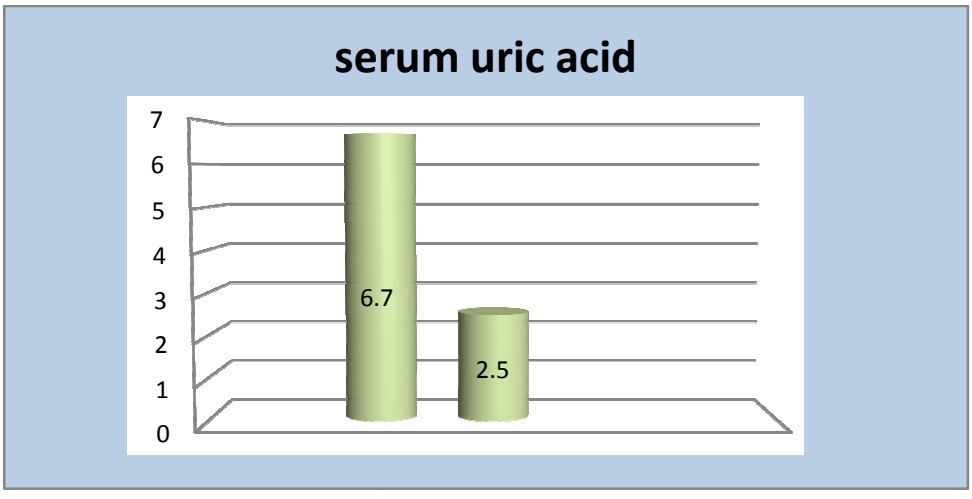


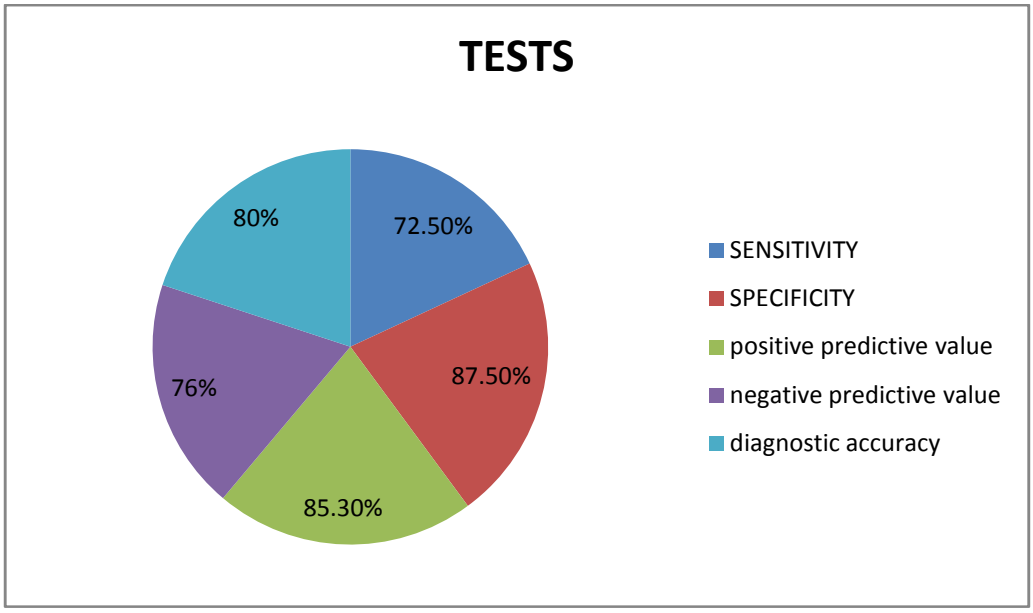
Table no 7 :Diagnostic value of serum uric acid in pre eclampsia

Serum uric acid (mg/dl)	Cases	Controls	Total
>6.2	34(68%)	10(20%)	44
<6.2	16(32%)	40(80%)	56
Total	50	50	100

P=0.0045 , significant.

- Sensitivity = 72.5 %
- Specificity = 87.5%
- Positive predictive value =85.3%
- Negative predictive value =76%
- Diagnostic accuracy = 80%

Pie chart no 8: Diagnostic value of serum uric acid in study groups



COMPARISON OF URINARY ALBUMIN LEVELS

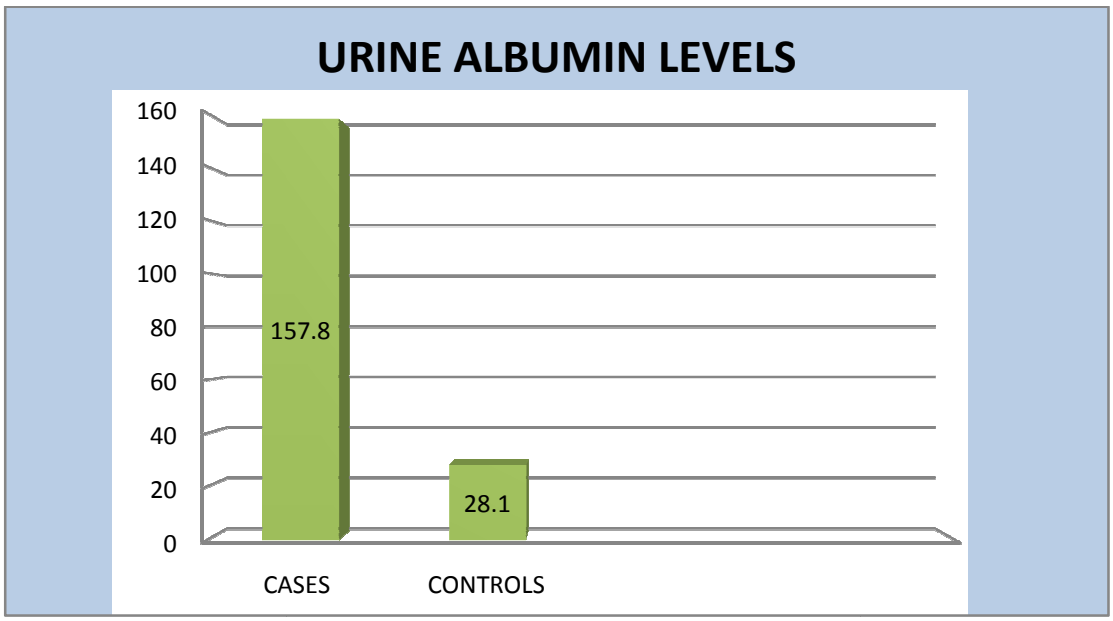
BETWEEN CASES AND CONTROLS

Table No 8 : Urine Albumin Levels In Study Groups

GROUPS		Urinary albumin (mg/ L)
Controls	Mean ±SD	28.1 ± 25.1
	Range	8.0 – 120.0
Cases	Mean ±SD	157.8 ± 48.7
	Range	62.2 – 260.4
CASES	MEAN differences	129.6
VS	't' value*	16.9
CONTROLS	'p' value	<0.001, HS.

*-unpaired test HS – highly significant.

Bar diagram no 9 : Urine albumin levels in cases and controls



The mean urinary albumin values found in the controls was 28.1±25.1 mg/dl, while in the cases it was 157.8 ± 48.7 mg/L. The mean difference between the two groups was 129.6 mg/day.

Stastical analysis using unpaired ‘t’ test showed that urinary albumin levels in the cases were significantly higher when compared to controls. The p value was highly significant ($p<0.001$) between the cases and controls.

URINARY CREATININE LEVELS

Table no 9: Urine Creatinine levels in study groups

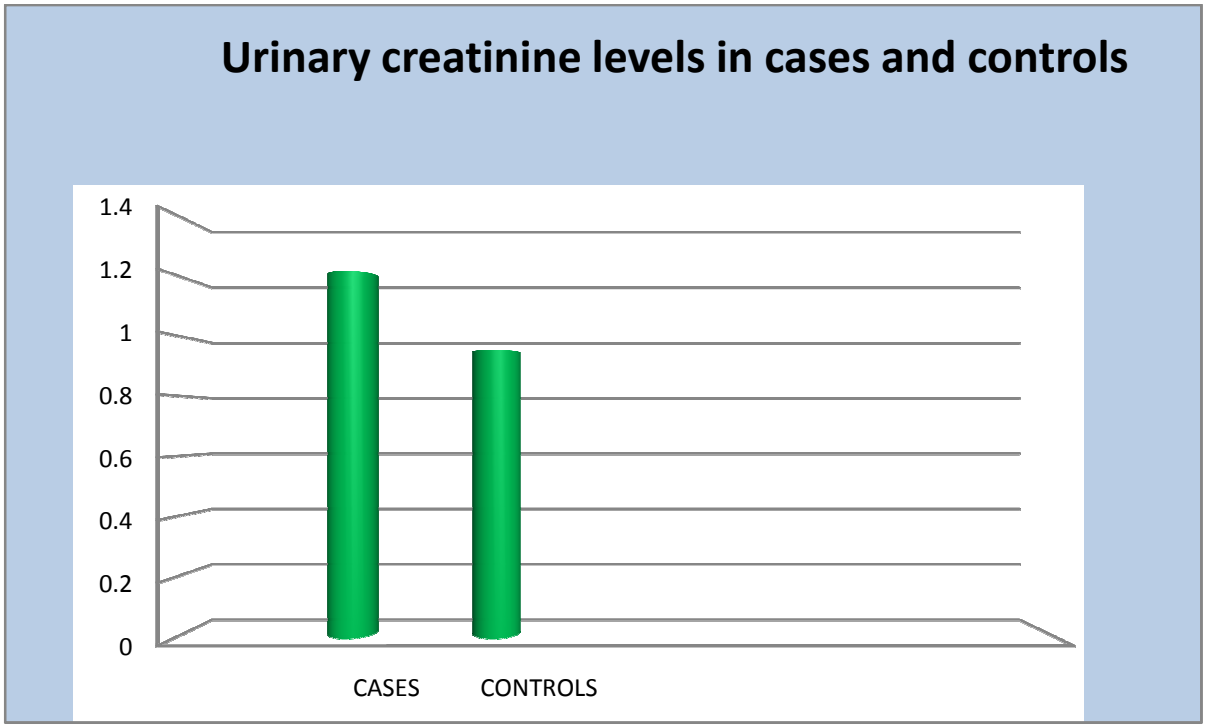
GROUPS		Urinary creatinine (gm/day)
Controls	Mean ±SD	0.95 ± 0.16
	Range	0.8 -1.6
Cases	Mean ±SD	1.21±0.37
	Range	0.80 – 1.88
CASES	MEAN differences	0.26
VS	't' value*	4.63
CONTROLS	'p' value	<0.001, HS.

*-unpaired test HS – highly significant.

The mean urinary creatinine values found in the controls was 0.95±0.16 gm/day, while in the cases it was 1.21 ±0.37 gm/day. The mean differences between the two group was 0.26 gm/day.

Statistical analysis using unpaired 't' test showed that the urinary creatinine levels in the cases were significantly higher when compared to controls. The p value was highly significant ($p<0.001$) between cases and controls.

Bar diagram no 10: Urinary creatinine levels in cases and controls



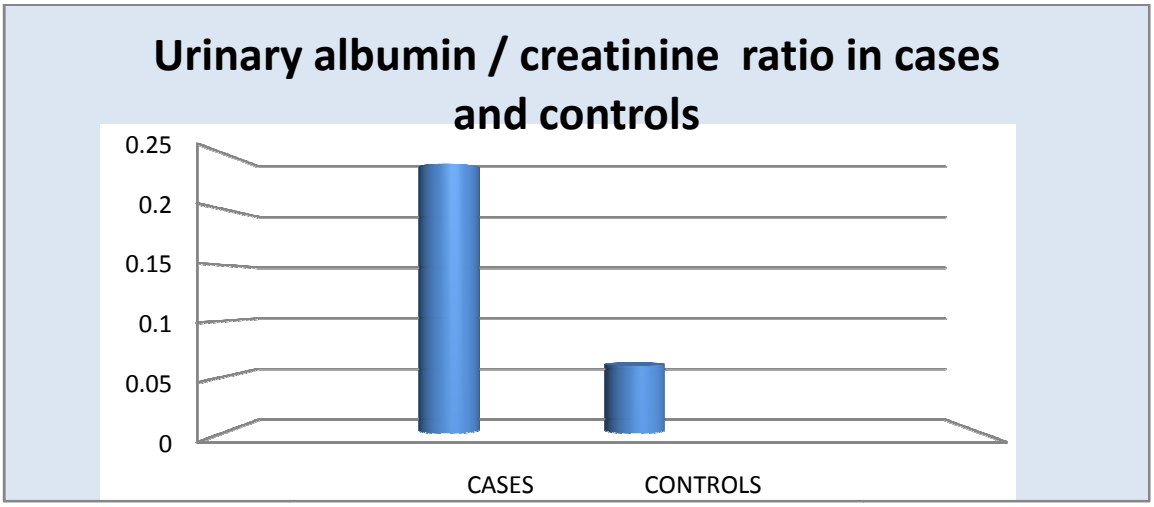
COMPARISON OF URINARY ALBUMIN / CREATININE RATIO BETWEEN CASES AND CONTROLS

Table no 10 : Urine Albumin / Creatinine ratio in study groups

GROUPS		Urinary albumin / Creatinine ratio
Controls	Mean ±SD	0.06±0.05
	Range	0.01-0.24
Cases	Mean ±SD	0.21±0.08
	Range	0.06-0.43
CASES	MEAN differences	0.15
VS	't' value*	10.3
CONTROLS	'p' value	<0.001, HS.
	CUT OFF VALUE	>0.14

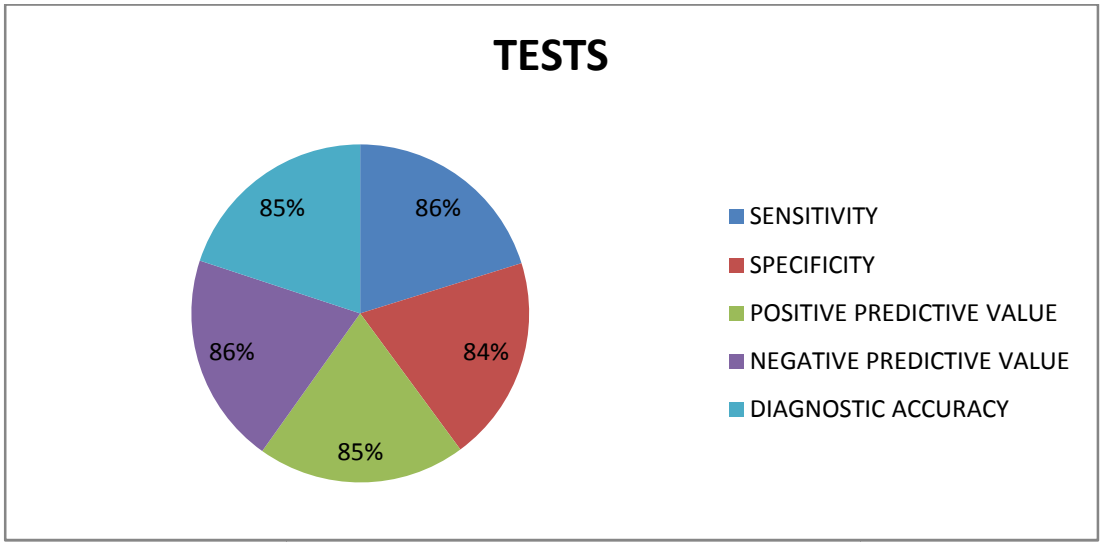
*-unpaired test HS – highly significant.

Bar diagram no 11 :Urine Albumin Creatinine ratio



- Sensitivity - 86%
- Specificity – 84%
- Positive predictive value – 85%
- Negative predictive value – 86%
- Diagnostic accuracy – 85%

Pie Chart No 12 : Diagnostic Value Of Urine Albumin / Creatinine Ratio



The mean Urinary Albumin : Creatinine ratio found in the controls was 0.06 ±0.05, while in cases it was 0.21 ± 0.08. The mean difference between the two group was 0.15.

Stastical analysis using unpaired ‘t’ test showed that the urinary albumin; creatinine ratio in the cases were significantly higher when compared to controls. The p values was highly significant ($p<0.001$) between cases and controls. The cut off value was taken as 0.14. values of more than 0.14 was found in the cases.

ONSET OF LABOUR

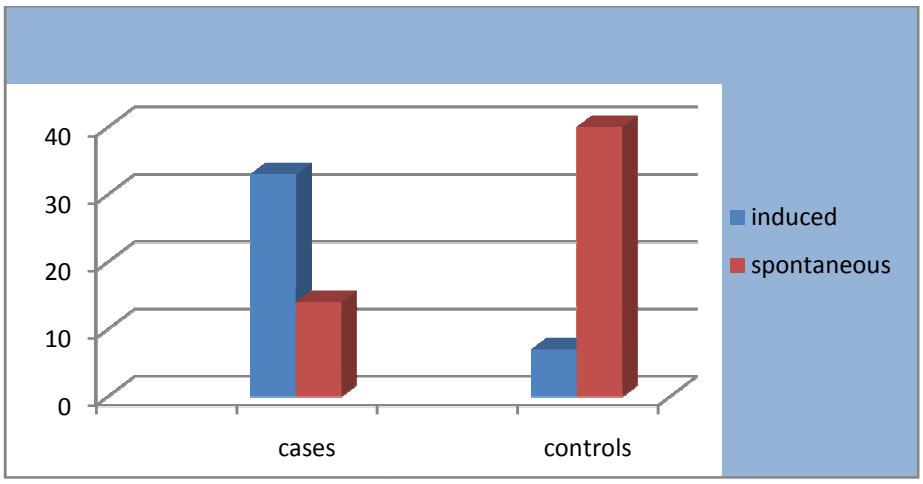
The onset of labour of cases and controls are shown in the table

Table no 11 : onset of labour

Onset	Cases	Controls	P value	Statistical significance
Induced	33(66%)	7(14%)	<0.001	High
Spontaneous	14(28%)	40(80%)	<0.001	High

Out of 50 patients in cases, 3 underwent elective caesarean. Out of remaining 47 patients in cases , 33(66%) were induced and 14(28%) went in to spontaneous labour. Out of 50 controls, 3 underwent elective caesarean section. Out of remaining 47 patients, 7 were induced and 40 went for spontaneous labour. There is a high statistical significance with respect to the onset of labour.

Bar diagram no 13 : showing onset of labour in study groups



MODE OF DELIVERY

The mode of delivery in the study groups are shown in the following table

Table no 12 : mode of delivery

Mode of delivery	Cases	Controls	P value	Statistical Significance
Caesarean	28(56%)	13(26%)	<0.01	High
Forceps	2(4%)	2(4%)	>0.05	None
vaginal	20(40%)	35(70%)	<0.05	High

Out of the 50 cases , 28 were delivered by caesarean, forceps were applied for 2 cases and the rest 20 were delivered vaginally.

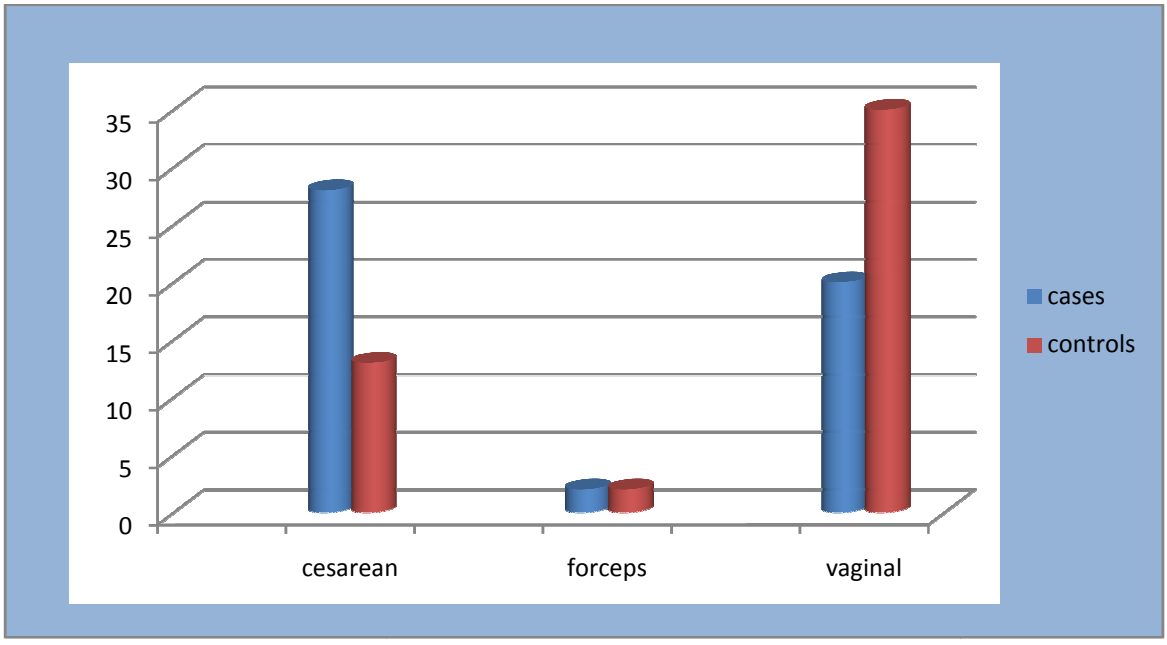
Out of 28 cesaresan in case group, 3 were planned for elective caesarean section, 1 due to abruption due to unfavourable cervix, 6 were due to IUGR with oligo hydraminos, 8 were due to failed induction, 4 due to fetal distress, 4 due to CPD, 1 due to HELLP syndrome and 1 due to failure to progression.

In controls, 13 patients were delivered by caesarean section, 2 were applied forceps, and the rest 35 were delivered vaginally.

In the control groups out of 13 cesarean section, 4 were due to failed induction, 4 were due to CPD, 2 were due to oligohydraminos and 3 were due to fetal distress.

Statistical analysis was done using fisher test, and there is a high statistical significance between the two groups with caesarean and vaginal mode of delivery. There is no significant statistical difference between the two groups with respect to forceps mode of delivery.

Bar diagram no 14 : showing mode of delivery in study groups



COMPLICATIONS

Table no 13 : complications

Complications	Cases	Controls
Abruption	1(2%)	0
Eclampsia	1(2%)	0
Imminent symptoms	7(14%)	0
IUGR	23(46%)	1(2%)

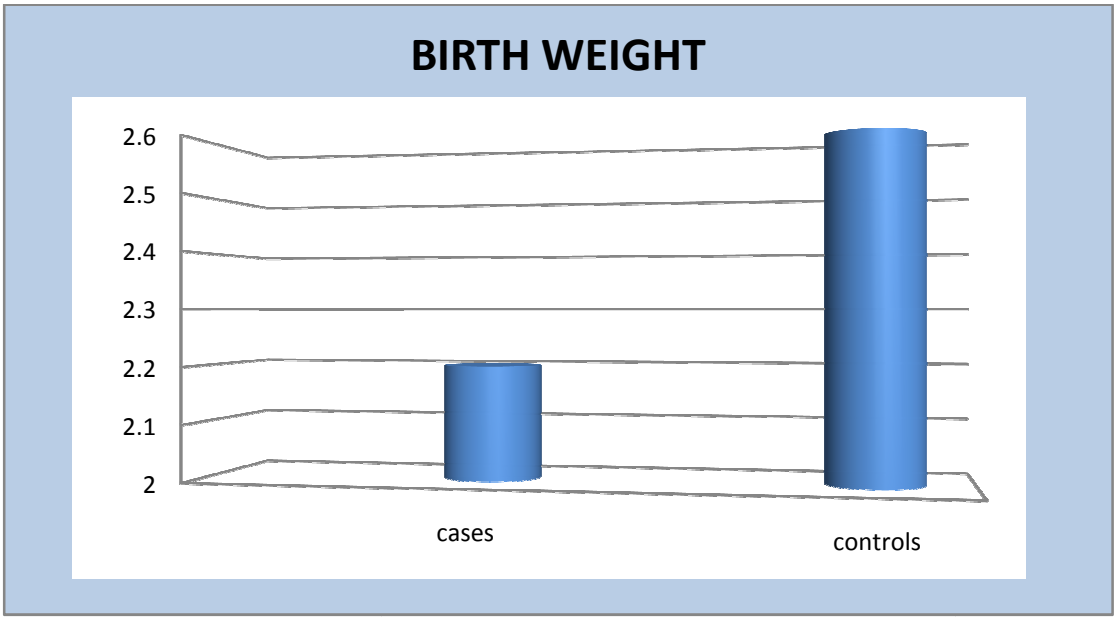
BIRTH WEIGHT

Table no 14 :Birth weight of babies in cases and controls

	Cases	Controls	't' value	'p' value	Statistical significance
Birth weight	2.2±0.5 kg	2.6±0.3 kg	4.028	<0.001	High

Mean birth weight of cases and controls were 2.2 ± 0.5 kg and 2.6 ± 0.3 kg respectively. There is high statistical significance between cases and controls.

Bar diagram no 15 :Birth weight of babies



PERINATAL OUTCOME

Table No 15: Perinatal Outcome

Parameters	Cases	Controls	P value	Significance
Apgar score < 7 at birth	27 (53%)	6(12%)	<0.001	High
Nicu admission	15(22%)	4(8%)	<0.001	High
Perinatal mortality	7(14%)	0	<0.05	High
Pre maturity	11(22%)	4(8%)	<0.001	High
Low birth weight	29(58%)	11(22%)	<0.001	High

Out of 50 cases, 15 babies in the case group were shifted to NICU due to very low birth weight, pre term, respiratory distress due to magnesium sulphate administration. Apgar score of <7 at 5 minutes was seen in 9 babies due to the above said reasons. Incidence of low birth weight was 58% and pre term was 22%.

Out of 50 controls, 2 babies had < 7 apgar score and NICU admission were 4, out of which 3 were due to meconium aspiration, one pre term and respiratory distress.. incidence of pre term was 8% and low birth weight in controls were 22%.

In case group,Seven cases (14%) of perinatal mortality.6 babies shifted to NICU due to low birth weight, birth asphyxia and respiratory distress. 1 baby was fresh still birth due to abruption.

There is statistically high significant difference in between cases and controls with respect to NICU admission and apgar score <7 at birth , perinatal mortality and low birth weight.

CORRELATION OF SEVERITY

The correlation of serum calcium levels with systolic blood pressure and diastolic blood pressure is shown in the following tables. There is a high statistical significant correlation between

- Serum calcium and systolic blood pressure (r -0.913)
- Serum calcium and diastolic blood pressure (r -0.8562)

Table no 16 : Correlation of serum calcium with blood pressure.

Parameter	**'r' value**	**'p' value**	**Statistical significance**
Systolic blood pressure (mm HG)	-0.9103	<0.001	High
Diastolic blood pressure(mm HG)	-0.8562	<0.001	High

r- karl pearson correlative co efficient

Chart no 16 :Correlation of serum calcium with systolic blood pressure

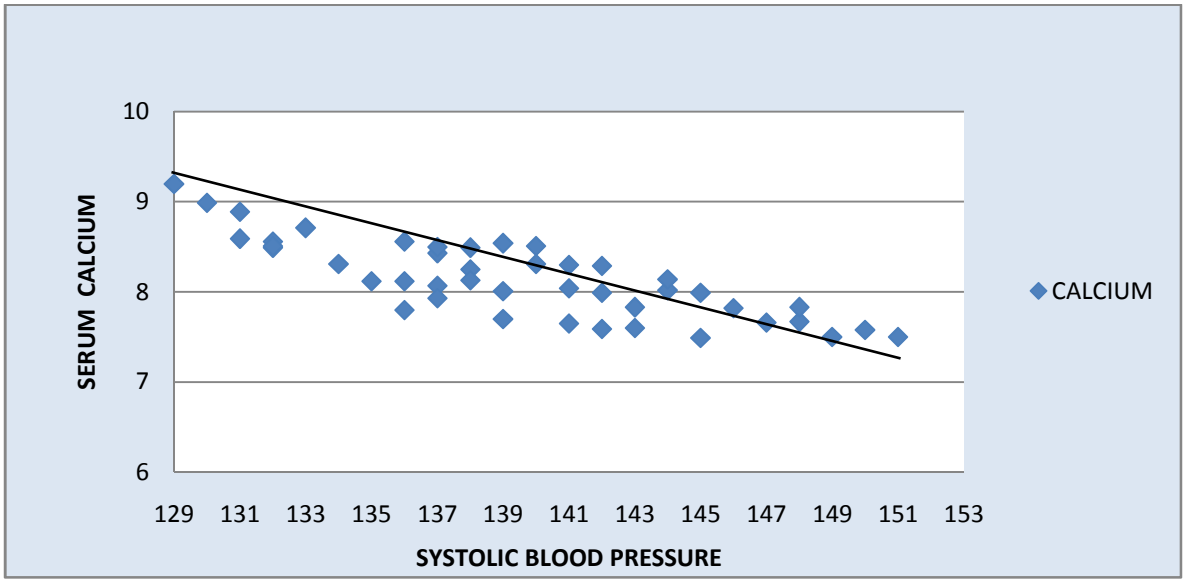
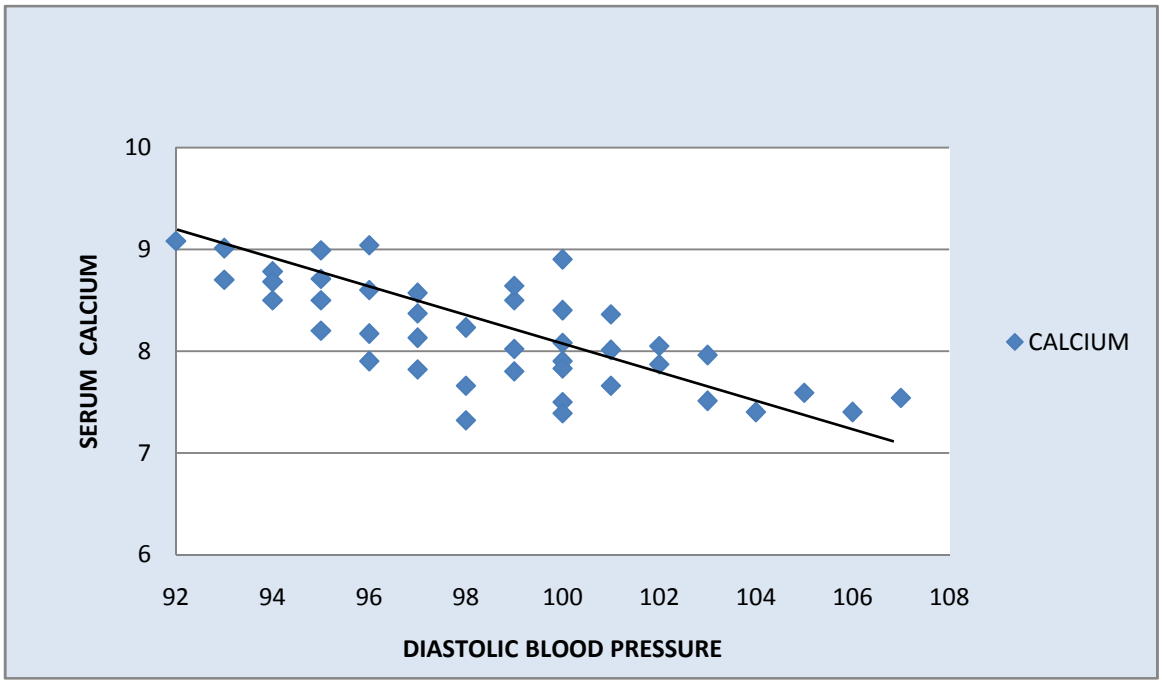


Chart no 17 :Correlation of serum calcium with diastolic blood pressure



DISCUSSION

DISCUSSION

The result of the present study showed that there is significant difference between the two groups that is the calcium levels were lower in patients with pre eclampsia than that of normal pregnant women.

COMPARISON OF SERUM CALCIUM

Authors	**Cases (mg/dl)**	**Controls (mg/dl)**	**Numbers in each group**	**P value**
Seema et al	8.3 ± 0.13	9.6 ± 0.18	50	<0.001
Suleyman et al	8.6 ± 0.5	9.4 ± 0.72	50	<0.001
Soe min et al	8.8 ± 0.7	9.8 ± 0.9	25	<0.001
Idougon et al	9.2 ± 1.02	9.8 ± 0.87	25	<0.001
Golmohammed et al	8.70 ± 0.58	8.97 ± 0.49	52	>0.05
Chanvity et al	8.70 ± 0.59	8.99 ± 0.31	50	>0.05
Sukonpan et al	9.0 ± 0.4	9.7 ±0.7	40	<0.0001
Present study	8.2 ± 0.6	9.7 ± 0.7	50	<0.001

The present study was similar to the results obtained by the above studies.

These datas suggested that calcium might be the cause of development of pre eclampsia. when serum calcium decreases, there is increase in intracellular

calcium which leads to constriction of smooth muscles and increase in vascular resistance.

There are some studies that may be contradictory, which proposed that the serum calcium level in pre eclampsia was not different from normal pregnancy. “ This may be a caused by a mislead between chronic hypertension or renal disease and pre eclamptic condition during pregnancy, the difference in the time of sample collection or the difference of dietary intake.”

“ In this study serum calcium were estimated after the onset of pre eclampsia and it is significantly lower than the normal pregnant women. now a days studies came out regarding the estimation of calcium at an early gestational age and it can be used as a predictor of pre eclampsia”

“The limitations of the study are that the dietary intake of calcium are not taken in to consideration “supplementation of calcium in pregnant women in developing country helps us in reducing the incidence of pre eclampsia “

Endothelial dysfunction is the predominant pathology which occurs as early as 8-18 weeks but the signs and symptoms occur in the late trimester. In order to arrest the progression of disease in the initial stages, there are various predictors of pre eclampsia have been prepared .proteinuria and alterations in calcium and uric acid metabolism are common features of various forms of hypertension.

There is statistically significant increase in the levels of serum uric acid in cases ($p = 0.0045$). The diagnostic accuracy was 80 % and there is a highly significant, positive correlation between serum uric acid and diastolic blood pressure.

This is in accordance with the study done by the salih f et al , who also showed that there is significant increase in serum uric acid levels in pre eclampsia and it was a good predictor of maternal disease progression and fetal outcome.

Bainbridge S A et al showed that there is a significant relation between hyperuricemia and pre eclampsia, where serum uric acid was a independent pathogenic agent.

Gulati R and Roberts J M et al showed that there is a significant increase in the serum uric acid level in pre eclampsia patients and associated with risks of adverse outcome. Koopmans C M et al , in their bivariate meta analysis , revealed that the measurements of serum uric acid was useful test to predict the maternal complications of preeclampsia.

To predict the maternal complications in the management of women with pre eclampsia. They also suggest that in patients with increased serum uric acid levels. Labour should be induced due to their increased risk of complications.

In the present study, the mean urinary albumin values found in the controls was 28.1±25.1 mg/dl, while in the cases it was 157.8 ± 48.7 mg/L. The present study showed that urinary albumin levels in the pre eclamptic women were significantly higher when compared to normal pregnant women. The p value was highly significant ($p<0.001$).

These findings are in accordance with the studies of Poon LCY et al, Daya sirohiwal et al, Misiani R et al, Hellen Rodriguez et al. Their findings are that the normotensive women who later developed hypertension in the pregnancy, was found to have micro albumin excreted in urine in a significant amount.

In the present study, the urinary microalbumin /creatinine ratio was higher in women with gestational hypertension when compared with normotensive pregnant women. the cut off value was 0.14. a ratio of more than 0.14 was seen in the women with gestational hypertension. This was statistically significant with a p value of <0.001.

This is in accordance with the studies done by Neithardt ABet.al, Jaschevatzky OE et.al, Risberg A et.al, Nisell H et.al, Misiani R et.al, Poon LCY et.al,Kok-min seow et.al, Frank P. Schubert et.al,Higby Kenneth et.al.

In our study, with a cut off value of 0.14 the ratio of microalbumin/creatininehas a sensitivity of 86%, specificity of 84%, positive

predictive value of 85%,negative predictive value of 86% and diagnostic accuracy of 85%.The most prevalent quantitative assessment of the amount of protein excretedin the urine for the diagnosis of pre-eclampsia is a 24- hour urine collection.

However,the collection and analysis of 24-hour urine specimens is cumbersome and time consuming for both patient and the laboratory. This has lead to the use of singlevoided urine protein/creatinine ratio to estimate proteinuria. This is because the ratioof 2 stable excretion rates, creatinine and protein would cancel out the time factorand thus provide a better estimate of 24-hour protein excretion.

Hence, themicroalbumin/creatinine ratio was used in our study to estimate microalbuminuria.Also few studies have suggested that a protein/creatinine ratio of <0.2 rules out thepresence of significant proteinuria (>300mg/L) which correlates well with our study.

In our study the mean value of urinary creatinine found in the controls are 0.95 ± 0.16 gm/day, while in the cases it was 1.21 ± 0.37 gm/day. It was statistically significant ($p<0.001$) between cases and controls.

In our study, the caesarean rate was 56% among the pre eclampsia patients. The caesarean rate in other similar studies were 72% in Tuffnell et al, 54% in Al Inizi et al, 79% in Sibai et al.

There is no maternal mortality in this present study. The complications were abruption in 1 case, eclampsia in 1 case, imminent ecalmpsia in 7 cases. The overall complications rate in our study is 18% which is statistically less when compared with various other studies. This is achieved through the close followup and monitoring of the patients.

In this study, the perinatal mortality was around 14% , NICU admissions were about 22%.

SUMMARY

SUMMARY

A study of strength of association between changes in serum calcium , serum uric acid , urine albumin – creatinine ratio and pre eclampsia and its impact on outcome.

This study was done at Thanjavur Medical College Hospital, Thanjavur.

- ✓ 50 women with pre eclampsia as cases and 50 normal healthy pregnant women as controls were selected for the study.
- ✓ There was a decrease in serum calcium levels and increase in serum uric acid in pre eclamptic patients when compared with normal healthy pregnant women. The changes in calcium and uric acid were statistically significant .
- ✓ The urinary albumin creatinine ratio in cases of pre eclampsia when compared to controls was statistically significant($p<0.01$).

The present study showed hypocalcemia and hyperuricemia in pre eclampsia, suggesting the role of calcium and uric acid in the etiology of pre eclampsia , though the exact mechanism remains to be elucidated.

The strength of association between these factors and pre eclampsia are very much significant. These factors are much useful in the earlier period of gestation in the screening of pre eclampsia.

In this study caesarean rates in the pregnant women are higher among the pre eclampsia patients. In this study there is no maternal mortality, CVA or

severe acute renal failure. Despite the use of magnesium sulphate and careful control of blood pressure e had, one case of eclampsia and 1 case of abruption with IUD. Among the perinatal outcome, incidence of IUGR babies, NICU admissions are more common among the babies of pre eclampsia.

CONCLUSION

CONCLUSION

But it remains to be known whether these changes are a cause and consequences of the disease. It is not clear which is the primary event that trigger the onset of hypertension in pre eclampsia.

Ongoing research shows abundant evidence that the pathophysiological changes of pre eclampsia are present long before the clinical presentation of the disease, which probably explains why all the management of PIH, other than the delivery are only palliative.

In this study, by the help of careful and close monitoring of the patients, the maternal mortality is avoided and maternal morbidity is greatly reduced.

The factors like serum calcium, serum uric acid and urine albumin/ creatinine ratio are strongly associated with pre eclampsia. These biochemical changes appears well before their clinical presentation.

Among Maternal mortality world wide, 10 -15 % were due to pre eclampisa and eclampsia. Despite advances in medical practice, pre eclampsia has remained a leading cause of maternal mortality throughout the world. Our hospital is a major referral centre. So there is relatively high prevalence of pre eclampsia in our population. Close and frequent observation of maternal and fetal status of pre eclampsia in a tertiary care centre, is associated with a good perinatal outcome and reduced risk of complications for the mother.

Thus it can be concluded that , the careful monitoring of these markers in pregnant women may help in the mortality and morbidity reduction and thereby helpful in the favourable outcome of the pregnancy.

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CONSENT FORM

I ..... hereby give consent to participate in the study conducted by **DR.M.KOKILAVANI,** post graduate in department of Obstetrics and Gynaecology, Thanjavur medical college & hospital, Thanjavur -613001 and to use my personal clinical data and result of investigation for the purpose of analysis and to study the nature of disease. I also give consent for further investigations.

Place : Signature of participant

Date :

PROFORMA

PROFORMA

I. Particulars

1. Name
2. Age
3. Religion
4. Address
5. Occupation
6. Educational status
7. Socio economic status
8. Date of admission
9. In patient / out patient number

II. **History :** Duration of amennorhoea, history suggestive of pre eclampsia

III. **Obstetric history** married life, consanguinity, obstetric index, history of present pregnancy

IV. **Menstrual history** : previous cycles, regularity, last menstrual period (LMP) and period of gestation

V. **Past history**: H/O hypertension, diabetes mellitus.

VI. **Family history** : h/o diabetes mellitus, hypertension, pre eclampsia in mother

VII. General physical examination

Height	pallor	thyroid
weight	icterus	breast
BMI	edema	spine

VIII. Vital data

Temperature	Resting Pulse Rate
Systolic BP	
Diastolic BP	Rate of respiration

IX. Systemic examination

1. Respiratory system
2. CVS
3. CNS
4. Per abdomen examination
   - Abdominal wall edema
   - Uterine size(gestational age)
   - Fetal heart rate and fetal movements

X. Investigations

Hb%	blood group	
urine albumin	urine creatinine	ratio
serum calcium	serum uric acid	

XI. Outcome measures

- ✓ Maternal complications : abruption imminent symptoms, eclampsia, IUGR.
- ✓ Onset of labour : induced or spontaneous.
- ✓ Mode of delivery : vaginal, caesarean and its indications, instrumental delivery.
- ✓ Baby details : birth weight, date of birth, APGAR score, NICU admission.

MASTER CHART

Key To Master Chart

1. Sl.no – serial number
2. OP/IP no - Outpatient/ Inpatient Number
3. POG - period of gestation
4. SBP - systolic blood pressure
5. DBP - diastolic blood pressure
6. Sr.Ca – serum calcium
7. Sr.UA – serum uric acid
8. U.Alb – urine albumin
9. U.Cre- urine creatinine
10. U.A/C – urine albumin/creatinine
11. COMP – complications
12. MOD – mode of delivery
13. BW – birth weight
14. igr- intrauterine growth retardation
15. oligos- oligohydraminos
16. im – imminent eclampsia
17. cs- caesarean
18. v- vaginal

MASTER CHART – CONTROL

Sl. No.	Name	Age	OP/IP	POG	Parity	SBP	DBP	Sr.Ca	Sr.UA	U.Alb	U.Cre	U.A/C	Comp	MOD	BW	A1	A5
1.	KARTHIKA	21	217621	28	PRIMI	128	78	10.2	3.95	26.12	0.83	0.04	-	0	2.9	7	9
2.	MAHESWARI	18	218253	29	PRIMI	130	72	10.6	4.63	18.23	0.82	0.03	-	v	3	8	10
3.	SARASWATHI	23	217832	32	MULTI	122	76	9.6	4.96	16.31	1	0.24	-	v	3.7	7	9
4.	LAKSHMI	19	2179116	30	PRIMI	110	70	8.5	5.03	10.81	0.89	0.16	-	v	2.8	6	10
5.	PARVATHI	23	2178262	28	PRIMI	130	78	8.9	6.91	10.81	0.96	0.02	-	v	2.6	8	10
6.	KALA	30	218242	29	MULTI	126	80	10.7	2.81	17.92	0.9	0.029	-	v	2.7	6	9
7.	MANIMEGALAI	32	217849	31	MULTI	124	84	9.8	3.76	14.01	0.84	0.025	-	v	2.9	7	10
8.	MEERA	24	218259	32	PRIMI	120	86	8.5	3.85	25.43	1.05	0.03	-	v	3.2	7	9
9.	BRINDHA	29	218654	28	MULTI	126	88	8.7	2.98	10.45	0.94	0.01	-	v	3.	7	10
10.	CHITRA	26	217959	30	PRIMI	122	70	9.6	3.58	10.92	0.82	0.02	-	v	2.8	7	9
11.	DEVIKA	20	269658	32	PRIMI	130	78	9.8	2.64	17.43	0.84	0.03	-	v	3.1	7	10
12.	ARCHANA	25	225849	28	PRIMI	110	76	9.3	4.51	22.43	0.8	0.04	-	v	2.5	7	10
13.	SARALA	29	217640	29	MULTI	110	70	9	5.08	19.4	0.94	0.03	-	Cs	2.7	7	9
14.	VEERALAKSHMI	31	217242	31	MULTI	128	72	9.6	5.13	26.19	0.9	0.03	-	v	2.2	7	10
15.	MEENA	34	218061	30	MULTI	120	82	9.8	6.31	18.81	0.96	0.03	-	Cs	2.8	7	9
16.	VIJAYA	22	217521	32	PRIMI	124	86	9	3.81	10.23	1.2	0.015	-	o	2.9	7	10
17.	UMA	35	216253	28	MULTI	130	88	9.2	6.14	19.01	1.04	0.023	-	Cs	2.6	5	10
18.	MARI	23	218261	29	PRIMI	110	80	9	5.98	24.08	0.98	0.034	-	Cs	2.8	7	10
19.	SOOSAI AMMAL	28	217267	32	PRIMI	118	82	9.6	2.59	28.16	1.6	0.043	-	v	2.4	7	10
20.	VANATHY	18	217521	31	PRIMI	110	80	9.4	3.95	14.23	0.89	0.013	-	v	3.1	6	10
21.	KUMUDHA	26	218651	30	MULTI	118	84	10.4	6.61	19.24	0.92	0.032	-	v	2.9	7	7
22.	KEERTHI	22	217451	28	PRIMI	100	88	9.6	4.81	22.46	0.84	0.036	-	v	2.8	7	10
23.	AMARAVATHY	27	217662	32	PRIMI	114	78	10.6	4.13	12.12	0.8	0.051	-	Cs	3.6	8	10
24.	VINITHA	19	217567	28	PRIMI	100	76	12	2.54	28.4	0.98	0.03	-	v	3	8	10
25.	SANGEETHA	23	218452	28	PRIMI	110	80	9	3.91	20.22	0.94	0.03	-	Cs	2.9	6	9

Sl. No.	Name	Age	OP/IP	POG	Parity	SBP	DBP	Sr.Ca	Sr.UA	U.Alb	U.Cre	U.A/C	Comp	MOD	BW	A1	A5
26.	MALA	21	218655	30	PRIMI	110	86	9.6	2.52	8.04	0.94	0.012	-	V	2.8	8	10
27.	VASUKI	22	218756	30	PRIMI	110	90	8.9	3.11	10.23	1	0.10.	-	V	3.1	8	10
28.	SEETHA	26	217769	32	MULTI	102	88	10.8	6.98	14.62	1.12	0.019	-	CS	2.9	8	10
29.	RAMYA	18	217821	31	PRIMI	109	90	10	4.16	29.16	0.82	0.053	-	V	2.5	8	10
30.	JAYALAKSHMI	29	217420	29	MULTI	100	90	10.6	4.81	42.03	0.89	0.07	-	V	2.8	8	9
31.	PRIYA	24	218521	28	PRIMI	110	86	10.2	4.12	18.26	1.22	0.06	-	V	2.5	7	10
32.	SAKUNTHALA	25	218650	30	MULTI	114	84	9	3.96	9.42	0.9	0.04	-	V	2.5	7	9
33.	VASANTHA	33	218424	32	MULTI	116	80	10.4	4.05	26.12	0.98	0.06	-	V	2.6	8	9
34.	DEVI	24	217626	29	PRIMI	120	82	10.4	6.16	14.88	1.36	0.09	-	V	3	8	10
35.	ANANDHI	19	217957	31	PRIMI	122	86	10.5	4.4	11.04	0.86	0.09	-	V	3.1	8	10
36.	VICHITRA	23	217856	30	PRIMI	134	90	9.5	4.81	13.29	1.2	0.037	-	CS	2.7	7	10
37.	MANGAMMA	22	218324	32	PRIMI	108	80	9.1	3.21	26.12	1.04	0.014	-	V	2.3	8	10
38.	RATHINA	22	217256	28	PRIMI	110	84	10.2	2.96	12.01	1.28	0.012	-	V	8.6	9	10
39.	PAPPAMMAL	19	218426	28	PRIMI	100	88	9.1	5.92	8.24	0.98	0.05	-	CS	3	9	9
40.	KURUVAMMA	35	218627	30	MULTI	110	78	9.3	3.01	24.12	0.8	0.03	-	V	2.9	8	10
41.	ANITHA	26	218523	32	MULTI	110	80	9.2	4.86	18.46	0.89	0.05	-	V	2.5	7	10
42.	MALARVIZHI	31	216273	31	MULTI	112	82	10.4	6.01	29.26	0.92	0.08	-	V	2.8	7	9
43.	BHUVANESWARI	32	221121	29	MULTI	122	86	10.3	3.88	46.04	0.9	0.06	-	CS	3	8	10
44.	GEETHA	20	217723	30	PRIMI	110	70	9.3	4.02	34.4	0.8	0.18	-	V	2.9	9	9
45.	VINOTHINI	28	217251	28	MULTI	108	70	10.4	3.56	96.23	0.8	0.15	-	V	3.1	9	8
46.	SRINATH	27	217621	29	MULTI	100	78	10.6	6.04	84.04	0.82	0.12	-	V	3.2	8	9
47.	NIRMALA	26	217851	32	MULTI	126	72	10.2	4.56	72.13	0.9	0.15	-	V	2.9	9	10
48.	BANUMATHI	27	217961	32	MULTI	130	88	9.1	5.40	80.42	0.8	0.16	-	CS	2.6	9	10
49.	INDHUMATHI	35	218962	28	MULTI	110	82	10	5.01	92.01	0.84	0.06	-	V	2.7	8	9
50.	THENMOZHI	18	218021	28	MULTI	128	80	9.2	3.98	30.16	0.8	0.21	-	CS	2.8	8	10

MASTER CHART - CASES

Sl. No.	Name	Age	OP/IP	DOA	Parity	SBP	DBP	Ca	VA	U.Ab	U.Cre	U.A/c	Comp	MOD	BW	A1	A5
1.	RADHA	21	209261	28	PRIMI	138	90	10.3	6.7	62.18	1.26	0.074	igr	v	1.2	4	6
2.	KAMALA	19	209178	30	PRIMI	140	98	8.1	7.1	78.42	1.88	0.062	igr	v	2	6	8
3.	VIJI	23	208248	29	MULTI	142	100	8	6.9	101.24	0.98	0.155		o	2.9	6	8
4.	SRIDEVI	18	209642	31	PRIMI	144	102	8.3	6.01	124.12	1.31	0.142		v	1.9	6	6
5.	RAJI	24	207245	32	PRIMI	152	110	8.1	7.8	132.42	1.45	0.137	igr	cs	1.0	2	4
6.	VANI	30	217628	30	MULTI	160	130	7.2	6.5	145.16	1.53	0.142	igr	cs	2.8	8	8
7.	JANAKI	26	208246	28	PRIMI	138	120	7.6	7.1	139.42	1.24	0.168	igr	v	2.9	6	8
8.	AMBIKA	24	207245	29	PRIMI	140	100	6.6	6.9	148.64	1.84	0.135	eclamp	cs	2.8	6	8
9.	SHENBAGAM	31	217720	32	MULTI	140	104	7.6	7.2	201.21	1.72	0.175		cs	2.1	0	0
10.	AANANDHI	23	208242	28	PRIMI	150	100	10	8.1	192.45	1.62	0.178	igr	v	2.2	6	8
11.	KAVITHA	20	207646	30	PRIMI	155	115	8.1	5.3	183.56	1.8	0.152		cs	3.0	8	9
12.	DEEPA	25	207847	31	PRIMI	150	100	8.7	6.8	168.18	1.78	0.141		cs	1.8	8	8
13.	SUMITHRA	35	217842	28	MULTI	150	100	8.2	6.0	245.12	1.82	0.202		cs	2.7	6	8
14.	RAMA	22	218241	29	PRIMI	140	90	8.6	6.8	155.62	1.62	0.138	igr, im	v	1.0	5	6
15.	DEVI	24	209842	32	PRIMI	162	138	8.5	8.0	172.46	0.96	0.269	igrc	cs	2.2	7	8
16.	RANI	27	202470	28	MULTI	140	92	6.8	5.9	79.12	1.62	0.073		cs	2.6	6	8
17.	PRIYA	23	202410	29	PRIMI	150	94	8.2	6.9	156.82	1.24	0.189	igr	v	1.3	5	7
18.	RAGANI	28	216470	30	MULTI	144	90	8.6	4.7	114.12	0.92	0.186		v	2.4	6	8
19.	MEGALA	20	211210	32	PRIMI	152	98	8.6	5.8	180.24	1.53	0.176		cs	3.4	8	9
20.	SATHYA	29	208210	28	MULTI	138	100	8.8	6.3	100.48	0.94	0.16	im	cs	2.5	9	9
21.	VANITHA	23	218210	28	PRIMI	140	98	7.9	6.7	128.26	1.23	0.156		v	9.00	8	9
22.	VALARMATHI	34	209260	29	MULTI	148	110	8.8	7.1	158.42	0.86	0.276	igr	v	1.1	6	8
23.	KALA	22	207216	30	PRIMI	150	110	8.2	7.6	172.12	0.9	0.286	igr. im	cs	1.5	7	6
24.	SHARMILA	21	206215	28	PRIMI	146	98	8	5.9	208.42	1.14	0.274	igr	cs	1.8	6	8
25.	VIMALA	31	219621	32	MULTI	160	100	7.4	5.9	236.08	1.26	0.281		v	2.6	8	10

Sl. No.	Name	Age	OP/IP	DOA	Parity	SBP	DBP	Ca	VA	U.Ab	U.Cre	U.A/c	Comp	MOD	BW	A1	A5
26.	DIVYA	21	228920	28	PRIMI	156	110	7.5	7.8	242.12	1.42	0.255	igr	cs	2.4	8	8
27.	VIDHYA	23	202965	29	MULTI	142	92	8.7	6.8	149.42	1.6	0.14	im	v	2.5	8	10
28.	PARVEEN	20	219625	30	PRIMI	140	90	8.7	8.4	182.64	0.9	0.301		cs	2.8	6	8
29.	NOORJAHAN	24	218735	28	PRIMI	150	110	7.7	5.3	212.12	0.88	0.361		o	2.6	7	8
30.	PALANIAMMAL	28	221360	32	MULTI	154	98	8.3	7.1	78.42	0.8	0.147	igr	v	1.2	7	8
31.	NADHIYA	25	231250	28	PRIMI	140	98	8.7	4.3	92.16	0.98	0.141		cs	3.2	8	9
32.	ILAVARASI	32	221069	32	MULTI	150	98	8.6	8.6	88.44	0.82	0.162	igr	fv	2.2	4	8
33.	MARY	22	217605	30	PRIMI	148	90	8	7.1	108.46	0.86	0.131		cs	2.5	8	8
34.	KAMATCHI	18	218302	29	PRIMI	150	110	9.3	4.3	112.42	0.98	0.196	igr	v	1.1	6	7
35.	VADIVU	27	219305	31	MULTI	148	100	8.8	6.9	118.23	0.94	0.182	igr	cs	2.4	8	8
36.	JULIE	23	208709	28	PRIMI	140	90	8.6	3.9	122.16	1.24	0.195		cs	3.4	6	8
37.	BANUMATHY	33	217302	28	MULTI	140	90	8.2	6.6	148.19	1.86	0.142	im	cs	2.2	6	8
38.	MALLIKA	22	216305	30	PRIMI	155	98	8.8	7.9	154.16	0.86	0.269		o	2.9	6	8
39.	KIRUTHIKA	24	218358	32	MULTI	144	96	8.6	8.0	198.49	0.92	0.323	igr	cs	2.4	8	9
40.	HARINI	29	205670	31	PRIMI	160	90	8.1	6.9	128.42	0.98	0.2		cs	2.4	6	8
41.	RANI	23	225790	29	PRIMI	150	110	7.8	6.4	200.16	1.16	0.26	igr	v	1.2	8	10
42.	JAMILABEGAM	19	218630	28	PRIMI	146	94	8.6	7.2	214.24	1.26	0.26		cs	2.5	5	8
43.	VISHALATCHI	30	217920	32	MULTI	160	110	7.6	6.8	140.26	0.9	0.23	igr	v	2.1	8	10
44.	NAGALAKSHMI	24	208020	28	PRIMI	144	90	7.6	8.0	158.42	0.88	0.27	igr	v	1.2	6	8
45.	VIJAYA	26	217201	28	PRIMI	130	94	9.3	6.4	246.02	1.88	0.20		v	2.4	8	10
46.	LAKSHMI	23	218920	29	PRIMI	140	98	9.1	7.2	148.16	0.8	0.28	igr	cs	2.1	4	10
47.	MARY	31	212035	30	MULTI	150	90	8.5	6.6	178.02	0.82	0.32		V	1.1	4	6
48.	JASMINE	19	218612	32	PRIMI	140	100	8.2	6.4	188.09	0.8	0.35	im	v	2.5	7	8
49.	NIVEDHA	23	207241	32	PRIMI	150	90	8.4	7.4	192.4	0.8	0.36		v	2.3	8	10
50.	SHYLAJA	35	217291	28	MULTI	140	90	9.0	8	180.2	0.92	0.26	igr	cs	2.7	8	8